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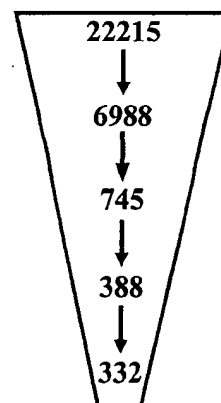
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(54) Title: BIOMARKERS AND METHODS FOR DETERMINING SENSITIVITY TO EPIDERMAL GROWTH FACTOR RECEPTOR MODULATORS

Gene Filtering Process

number of probesets

- Step 1: log-transform transcription data
- Step 2: remove probesets with colon tumor Max intensity < 3.477
- Step 3: remove probesets with colon tumor VARP < 0.1
- Step 4: remove probesets with colon cell line Max intensity < 3.477
- Step 5: remove probesets with colon cell line VARP < 0.1
- Step 6: perform two-sided T-test on colon cell line transcription data



(57) Abstract: EGFR biomarkers useful in a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises (a) exposing the mammal to the EGFR modulator and (b) measuring in the mammal the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in (b) compared to the level of the biomarker in a mammal that has not been exposed to the EGFR modulator indicates that the mammal will respond therapeutically to the method of treating cancer.

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BIOMARKERS AND METHODS FOR DETERMINING SENSITIVITY TO EPIDERMAL GROWTH FACTOR RECEPTOR MODULATORS

5 FIELD OF THE INVENTION

The present invention relates generally to the field of pharmacogenomics, and more specifically to methods and procedures to determine sensitivity in patients to allow the development of individualized genetic profiles which aid in treating diseases and disorders based on patient response at a molecular level.

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BACKGROUND OF THE INVENTION:

Cancer is a disease with extensive histoclinical heterogeneity. Although conventional histological and clinical features have been correlated to prognosis, the same apparent prognostic type of tumors varies widely in its responsiveness to therapy and consequent survival of the patient.

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New prognostic and predictive markers, which would facilitate an individualization of therapy for each patient, are needed to accurately predict patient response to treatments, such as small molecule or biological molecule drugs, in the clinic. The problem may be solved by the identification of new parameters that could better predict the patient's sensitivity to treatment. The classification of patient samples is a crucial aspect of cancer diagnosis and treatment. The association of a patient's response to a treatment with molecular and genetic markers can open up new opportunities for treatment development in non-responding patients, or distinguish a treatment's indication among other treatment choices because of higher confidence in the efficacy. Further, the pre-selection of patients who are likely to respond well to a medicine, drug, or combination therapy may reduce the number of patients needed in a clinical study or accelerate the time needed to complete a clinical development program (M. Cockett et al., 2000, *Current Opinion in Biotechnology*, 11:602-609).

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The ability to predict drug sensitivity in patients is particularly challenging because drug responses reflect not only properties intrinsic to the target cells, but also a host's metabolic properties. Efforts to use genetic information to predict drug sensitivity have primarily focused on individual genes that have broad effects, such as the multidrug resistance genes, *mdr1* and *mrp1* (P. Sonneveld, 2000, *J. Intern. Med.*, 247:521-534).

30

The development of microarray technologies for large scale characterization of gene mRNA expression pattern has made it possible to systematically search for molecular markers and to categorize cancers into distinct subgroups not evident by traditional histopathological methods (J. Khan et al., 1998, *Cancer Res.*, 58:5009-5013; A.A. Alizadeh et al., 2000, *Nature*, 403:503-511; M. Bittner et al., 2000, *Nature*, 406:536-540; J. Khan et al., 2001, *Nature Medicine*, 7(6):673-679; and T.R. Golub et al., 1999, *Science*, 286:531-537; U. Alon et al., 1999, *Proc. Natl. Acad. Sci. USA*, 96:6745-6750). Such technologies and molecular tools have made it possible to monitor the expression level of a large number of transcripts within a cell population at any given time (see, e.g., Schena et al., 1995, *Science*, 270:467-470; Lockhart et al., 1996, *Nature Biotechnology*, 14:1675-1680; Blanchard et al., 1996, *Nature Biotechnology*, 14:1649; U.S. Patent No. 5,569,588 to Ashby et al.).

Recent studies demonstrate that gene expression information generated by microarray analysis of human tumors can predict clinical outcome (L.J. van't Veer et al., 2002, *Nature*, 415:530-536; M. West et al., 2001, *Proc. Natl. Acad. Sci. USA*, 98:11462-11467; T. Sorlie et al., 2001, *Proc. Natl. Acad. Sci. USA*, 98:10869-10874; M. Shipp et al., 2002, *Nature Medicine*, 8(1):68-74). These findings bring hope that cancer treatment will be vastly improved by better predicting the response of individual tumors to therapy.

Needed are new and alternative methods and procedures to determine drug sensitivity in patients to allow the development of individualized genetic profiles which are necessary to treat diseases and disorders based on patient response at a molecular level.

SUMMARY OF THE INVENTION:

The invention provides methods and procedures for determining patient sensitivity to one or more Epidermal Growth Factor Receptor (EGFR) modulators. The invention also provides methods of determining or predicting whether an individual requiring therapy for a disease state such as cancer will or will not respond to treatment, prior to administration of the treatment, wherein the treatment comprises one or more EGFR modulators. The one or more EGFR modulators are compounds that can be selected from, for example, one or more EGFR specific ligands, one or

more small molecule EGFR inhibitors, or one or more EGFR binding monoclonal antibodies.

In one aspect, the invention provides a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in the mammal
5 the level of at least one biomarker selected from the biomarkers of Table 1; (b) exposing the mammal to the EGFR modulator; (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of
10 the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

As used herein, respond therapeutically refers to the alleviation or abrogation of the cancer. This means that the life expectancy of an individual affected with the cancer will be increased or that one or more of the symptoms of the cancer will be
15 reduced or ameliorated. The term encompasses a reduction in cancerous cell growth or tumor volume. Whether a mammal responds therapeutically can be measured by many methods well known in the art, such as PET imaging.

The mammal can be, for example, a human, rat, mouse, dog rabbit, pig sheep, cow, horse, cat, primate, or monkey.

20 The method of the invention can be, for example, an in vitro method and wherein the at least one biomarker is measured in at least one mammalian biological sample from the mammal. The biological sample can comprise, for example, at least one of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, skin, hair follicle, or tumor tissue.

25 In another aspect, the invention provides a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) exposing the mammal to the EGFR modulator; (b) following the exposing of step (a), measuring in the mammal the level of the at least one biomarker selected from the biomarkers of
30 Table 1, wherein a difference in the level of the at least one biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been

exposed to said EGFR modulator, indicates that the mammal will respond therapeutically to said method of treating cancer.

In yet another aspect, the invention provides a method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1; (b) exposing the mammal to the EGFR modulator; (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

In another aspect, the invention provides a method for determining whether a compound inhibits EGFR activity in a mammal, comprising: (a) exposing the mammal to the compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1, wherein a difference in the level of said biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said compound, indicates that the compound inhibits EGFR activity in the mammal.

In yet another aspect, the invention provides a method for determining whether a mammal has been exposed to a compound that inhibits EGFR activity, comprising (a) exposing the mammal to the compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1, wherein a difference in the level of said biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said compound, indicates that the mammal has been exposed to a compound that inhibits EGFR activity.

In another aspect, the invention provides a method for determining whether a mammal is responding to a compound that inhibits EGFR activity, comprising (a) exposing the mammal to the compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1, wherein a difference in the level of said biomarker measured

in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits EGFR activity.

As used herein, "responding" encompasses responding by way of a biological and cellular response, as well as a clinical response (such as improved symptoms, a therapeutic effect, or an adverse event), in a mammal

The invention also provides an isolated biomarker selected from the biomarkers of Table 1. The biomarkers of the invention comprise sequences selected from the nucleotide and amino acid sequences provided in Table 1 and the Sequence Listing, as well as fragments and variants thereof.

The invention also provides a biomarker set comprising two or more biomarkers selected from the biomarkers of Table 1.

The invention also provides kits for determining or predicting whether a patient would be susceptible or resistant to a treatment that comprises one or more EGFR modulators. The patient may have a cancer or tumor such as, for example, a colon cancer or tumor.

In one aspect, the kit comprises a suitable container that comprises one or more specialized microarrays of the invention, one or more EGFR modulators for use in testing cells from patient tissue specimens or patient samples, and instructions for use. The kit may further comprise reagents or materials for monitoring the expression of a biomarker set at the level of mRNA or protein.

In another aspect, the invention provides a kit comprising two or more biomarkers selected from the biomarkers of Table 1.

In yet another aspect, the invention provides a kit comprising at least one of an antibody and a nucleic acid for detecting the presence of at least one of the biomarkers selected from the biomarkers of Table 1. In one aspect, the kit further comprises instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits EGFR activity. In another aspect, the instructions comprise the steps of (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1, (b) exposing the mammal to the compound, (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker,

wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

5 The invention also provides screening assays for determining if a patient will be susceptible or resistant to treatment with one or more EGFR modulators.

The invention also provides a method of monitoring the treatment of a patient having a disease treatable by one or more EGFR modulators.

10 The invention also provides individualized genetic profiles which are necessary to treat diseases and disorders based on patient response at a molecular level.

The invention also provides specialized microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, comprising one or more biomarkers having expression profiles that correlate with either sensitivity or resistance to one or more EGFR modulators.

15 The invention also provides antibodies, including polyclonal or monoclonal, directed against one or more biomarkers of the invention.

The invention will be better understood upon a reading of the detailed description of the invention when considered in connection with the accompanying figures.

20

BRIEF DESCRIPTION OF THE FIGURES:

FIG. 1 illustrates the gene filtering process.

FIG. 2 illustrates the cell line filtering process.

FIG. 3 illustrates the cell line IC50 data.

25 FIG. 4 illustrates the T-test Results I.

FIG. 5 illustrates the T-test Results II.

FIG. 6 illustrates the T-test Results III.

DETAILED DESCRIPTION OF THE INVENTION:

30 The invention provides biomarkers that respond to the modulation of a specific signal transduction pathway and also correlate with EGFR modulator sensitivity or resistance. These biomarkers can be employed for predicting response

to one or more EGFR modulators. In one aspect, the biomarkers of the invention are those provided in Table 1 and the Sequence Listing, including both polynucleotide and polypeptide sequences.

5

TABLE 1 - BIOMARKERS

Unigene title and SEQ ID NOS:	Affymetrix Description	Affymetrix Probe Set
Cadherin 17, LI cadherin (liver-intestine) SEQ ID NOS:1 (nucleotide) and 67 (amino acid)	gb:U07969.1 /DEF=Human intestinal peptide-associated transporter HPT-1 mRNA, complete cds. /FEA=mRNA /PROD=intestinal peptide-associated transporter HPT-1 /DB_XREF=gi:483391 /UG=Hs.89436 cadherin 17, LI cadherin (liver-intestine) /FL=gb:NM_004063.1 gb:U07969.1	209847_at
Carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen) SEQ ID NOS:2 (nucleotide) and 68 (amino acid)	gb:BC005008.1 /DEF=Homo sapiens, carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen), clone MGC:10467, mRNA, complete cds. /FEA=mRNA /PROD=carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen) /DB_XREF=gi:13477106 /UG=Hs.73848 carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen) /FL=gb:BC005008.1 gb:M18216.1 gb:M29541.1 gb:NM_002483.1	203757_s_at
Carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen) SEQ ID NOS:3 (nucleotide) and 69 (amino acid)	gb:M18728.1 /DEF=Human nonspecific crossreacting antigen mRNA, complete cds. /FEA=mRNA /GEN=NCA; NCA; NCA /PROD=non-specific cross reacting antigen /DB_XREF=gi:189084 /FL=gb:M18728.1	211657_at
Lectin, galactoside-binding, soluble, 1 (galectin 1) SEQ ID NOS:4 (nucleotide) and 70 (amino acid)	gb:NM_002305.2 /DEF=Homo sapiens lectin, galactoside-binding, soluble, 1 (galectin 1) (LGALS1), mRNA. /FEA=mRNA /GEN=LGALS1 /PROD=beta-galactosidase binding lectin precursor /DB_XREF=gi:6006015 /UG=Hs.227751 lectin, galactoside-binding, soluble, 1 (galectin 1)	201105_at

	/FL=gb:BC001693.1 gb:J04456.1 gb:NM_002305.2	
Transmembrane protease, serine 2 SEQ ID NOS:5 (nucleotide) and 71 (amino acid)	gb:AF270487.1 /DEF=Homo sapiens androgen-regulated serine protease TMPRSS2 precursor (TMPRSS2) mRNA, complete cds. /FEA=mRNA /GEN=TMPRSS2 /PROD=androgen- regulated serine protease TMPRSS2precursor /DB_XREF=gi:13540003 /FL=gb:AF270487.1	211689_s_at
Mucin 5, subtypes A and C, tracheobronchial/gastric SEQ ID NOS:6 (nucleotide), 7 (nucleotide) and 72 (amino acid)	Consensus includes gb:AW192795 /FEA=EST /DB_XREF=gi:6471494 /DB_XREF=est:xl51d08.x1 /CLONE=IMAGE:2678223 /UG=Hs.103707 apomucin	214303_x_at
3-hydroxy-3- methylglutaryl- Coenzyme A synthase 2 (mitochondrial) SEQ ID NOS:8 (nucleotide) and 73 (amino acid)	gb:NM_005518.1 /DEF=Homo sapiens 3- hydroxy-3-methylglutaryl-Coenzyme A synthase 2 (mitochondrial) (HMGCS2), mRNA. /FEA=mRNA /GEN=HMGCS2 /PROD=3-hydroxy-3-methylglutaryl- Coenzyme A synthase 2(mitochondrial) /DB_XREF=gi:5031750 /UG=Hs.59889 3- hydroxy-3-methylglutaryl-Coenzyme A synthase 2 (mitochondrial) /FL=gb:NM_005518.1	204607_at
Interferon-stimulated protein, 15 kDa SEQ ID NOS:9 (nucleotide) and 74 (amino acid)	gb:NM_005101.1 /DEF=Homo sapiens interferon-stimulated protein, 15 kDa (ISG15), mRNA. /FEA=mRNA /GEN=ISG15 /PROD=interferon- stimulated protein, 15 kDa /DB_XREF=gi:4826773 /UG=Hs.833 interferon-stimulated protein, 15 kDa /FL=gb:M13755.1 gb:NM_005101.1	205483_s_at
Dopa decarboxylase (aromatic L-amino acid decarboxylase) SEQ ID NOS:10 (nucleotide) and 75 (amino acid)	gb:NM_000790.1 /DEF=Homo sapiens dopa decarboxylase (aromatic L-amino acid decarboxylase) (DDC), mRNA. /FEA=mRNA /GEN=DDC /PROD=dopa decarboxylase (aromatic L-amino aciddecarboxylase) /DB_XREF=gi:4503280 /UG=Hs.150403 dopa decarboxylase (aromatic L-amino acid decarboxylase) /FL=gb:BC000485.1 gb:M76180.1 gb:M88700.1 gb:NM_000790.1	205311_at

<p>Serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1</p> <p>SEQ ID NOS:11 (nucleotide) and 76 (amino acid)</p>	<p>gb:NM_000602.1 /DEF=Homo sapiens serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1 (SERPINE1), mRNA. /FEA=mRNA /GEN=SERPINE1 /PROD=serine (or cysteine) proteinase inhibitor, cladeE (nexin, plasminogen activator inhibitor type 1), member1 /DB_XREF=gi:10835158 /UG=Hs.82085 serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1 /FL=gb:NM_000602.1 gb:M16006.1</p>	202628_s_at
<p>FXFD domain-containing ion transport regulator 3</p> <p>SEQ ID NOS:12 (nucleotide) and 77 (amino acid)</p>	<p>gb:BC005238.1 /DEF=Homo sapiens, FXFD domain-containing ion transport regulator 3, clone MGC:12265, mRNA, complete cds. /FEA=mRNA /PROD=FXFD domain-containing ion transport regulator3 /DB_XREF=gi:13528881 /UG=Hs.301350 FXFD domain-containing ion transport regulator 3 /FL=gb:NM_005971.2 gb:BC005238.1</p>	202489_s_at
<p>Putative integral membrane transporter</p> <p>SEQ ID NOS:13 (nucleotide) and 78 (amino acid)</p>	<p>gb:NM_018407.1 /DEF=Homo sapiens putative integral membrane transporter (LC27), mRNA. /FEA=mRNA /GEN=LC27 /PROD=putative integral membrane transporter /DB_XREF=gi:8923827 /FL=gb:NM_018407.1</p>	208029_s_at
<p>Protease inhibitor 3, skin-derived (SKALP)</p> <p>SEQ ID NOS:14 (nucleotide) and 79 (amino acid)</p>	<p>gb:NM_002638.1 /DEF=Homo sapiens protease inhibitor 3, skin-derived (SKALP) (PI3), mRNA. /FEA=mRNA /GEN=PI3 /PROD=protease inhibitor 3, skin-derived (SKALP) /DB_XREF=gi:4505786 /UG=Hs.112341 protease inhibitor 3, skin-derived (SKALP) /FL=gb:NM_002638.1</p>	203691_at
<p>Caudal type homeo box transcription factor 2</p> <p>SEQ ID NOS:15 (nucleotide) and 80 (amino acid)</p>	<p>gb:U51096.1 /DEF=Human homeobox protein Cdx2 mRNA, complete cds. /FEA=mRNA /PROD=homeobox protein Cdx2 /DB_XREF=gi:1777773 /UG=Hs.77399 caudal type homeo box transcription factor 2 /FL=gb:U51096.1 gb:NM_001265.1</p>	206387_at
<p>Fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)</p>	<p>gb:NM_000142.2 /DEF=Homo sapiens fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism) (FGFR3), transcript variant 1, mRNA.</p>	204379_s_at

SEQ ID NOS:16 (nucleotide) and 81 (amino acid)	/FEA=mRNA /GEN=FGFR3 /PROD=fibroblast growth factor receptor 3, isoform 1 precursor /DB_XREF=gi:13112046 /UG=Hs.1420 fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism) /FL=gb:NM_000142.2 gb:M58051.1	
Hypothetical protein PP1665 SEQ ID NOS:17 (nucleotide), 18 (nucleotide) and 82 (amino acid)	Consensus includes gb:AL041124 /FEA=EST /DB_XREF=gi:5410060 /DB_XREF=est:DKFZp434D0316_s1 /CLONE=DKFZp434D0316 /UG=Hs.6748 hypothetical protein PP1665	213343_s_at
Protease inhibitor 3, skin-derived (SKALP) SEQ ID NOS:19 (nucleotide) and 83 (amino acid)	Cluster Incl. L10343:Huma elafin gene, complete cds /cds=(516,869) /gb=L10343 /gi=190337 /ug=Hs.112341 /len=871	41469_at
A kinase (PRKA) anchor protein (gravin) 12 SEQ ID NOS:20 (nucleotide) and 84 (amino acid)	gb:AB003476.1 /DEF=Homo sapiens mRNA for gravin, complete cds. /FEA=mRNA /PROD=gravin /DB_XREF=gi:2081606 /UG=Hs.788 A kinase (PRKA) anchor protein (gravin) 12 /FL=gb:AB003476.1	210517_s_at
Lymphocyte antigen 75 SEQ ID NOS:21 (nucleotide) and 85 (amino acid)	gb:NM_002349.1 /DEF=Homo sapiens lymphocyte antigen 75 (LY75), mRNA. /FEA=mRNA /GEN=LY75 /PROD=lymphocyte antigen 75 /DB_XREF=gi:4505052 /UG=Hs.153563 lymphocyte antigen 75 /FL=gb:AF011333.1 gb:AF064827.1 gb:NM_002349.1	205668_at
Mucin 5, subtypes A and C, tracheobronchial/gastric SEQ ID NOS:22 (nucleotide)	Consensus includes gb:AI521646 /FEA=EST /DB_XREF=gi:4435781 /DB_XREF=est:to66a06.x1 /CLONE=IMAGE:2183218 /UG=Hs.102482 mucin 5, subtype B, tracheobronchial	214385_s_at
Metallothionein 1G SEQ ID NOS:23 (nucleotide) and 86 (amino acid)	gb:NM_005950.1 /DEF=Homo sapiens metallothionein 1G (MT1G), mRNA. /FEA=mRNA /GEN=MT1G /PROD=metallothionein 1G /DB_XREF=gi:10835229 /UG=Hs.173451 metallothionein 1G /FL=gb:NM_005950.1	204745_x_at
Tumor necrosis factor	gb:NM_003823.1 /DEF=Homo sapiens	206467_x_at

receptor superfamily, member 6b, decoy SEQ ID NOS:24 (nucleotide) and 87 (amino acid)	tumor necrosis factor receptor superfamily, member 6b, decoy (TNFRSF6B), mRNA. /FEA=mRNA /GEN=TNFRSF6B /PROD=decoy receptor 3 /DB_XREF=gi:4507584 /UG=Hs.278556 tumor necrosis factor receptor superfamily, member 6b, decoy /FL=gb:AF104419.1 gb:NM_003823.1 gb:AF134240.1 gb:AF217794.1	
Mucin 3B SEQ ID NOS:25 (nucleotide) and 88 (amino acid)	Consensus includes gb:AB038783.1 /DEF=Homo sapiens MUC3B mRNA for intestinal mucin, partial cds. /FEA=mRNA /GEN=MUC3B /PROD=intestinal mucin /DB_XREF=gi:9929917 /UG=Hs.129782 mucin 3A, intestinal	214898_x_at
Metallothionein 1X SEQ ID NOS:26 (nucleotide) and 89 (amino acid)	gb:NM_005952.1 /DEF=Homo sapiens metallothionein 1X (MT1X), mRNA. /FEA=CDS /GEN=MT1X /PROD=metallothionein 1X /DB_XREF=gi:10835231 /UG=Hs.278462 metallothionein 1X /FL=gb:NM_005952.1	208581_x_at
GRO3 oncogene SEQ ID NOS:27 (nucleotide) and 90 (amino acid)	gb:NM_002090.1 /DEF=Homo sapiens GRO3 oncogene (GRO3), mRNA. /FEA=mRNA /GEN=GRO3 /PROD=GRO3 oncogene /DB_XREF=gi:4504156 /UG=Hs.89690 GRO3 oncogene /FL=gb:M36821.1 gb:NM_002090.1	207850_at
Transforming growth factor, beta-induced, 68kD SEQ ID NOS:28 (nucleotide) and 91 (amino acid)	gb:NM_000358.1 /DEF=Homo sapiens transforming growth factor, beta-induced, 68kD (TGFB1), mRNA. /FEA=mRNA /GEN=TGFB1 /PROD=transforming growth factor, beta-induced, 68kD /DB_XREF=gi:4507466 /UG=Hs.118787 transforming growth factor, beta-induced, 68kD /FL=gb:BC000097.1 gb:BC004972.1 gb:M77349.1 gb:NM_000358.1	201506_at
Bone morphogenetic protein 7 (osteogenic protein 1) SEQ ID NOS:29 (nucleotide) and 92 (amino acid)	gb:M60316.1 /DEF=Human transforming growth factor-beta (tgf-beta) mRNA, complete cds. /FEA=mRNA /GEN=tgf- beta /PROD=transforming growth factor- beta /DB_XREF=gi:339563 /UG=Hs.170195 bone morphogenetic protein 7 (osteogenic protein 1) /FL=gb:M60316.1 gb:NM_001719.1	209591_s_at
Annexin A10 SEQ ID NOS:30	gb:AF196478.1 /DEF=Homo sapiens annexin 14 (ANX14) mRNA, complete cds. /FEA=mRNA /GEN=ANX14	210143_at

(nucleotide) and 93 (amino acid)	/PROD=annexin 14 /DB_XREF=gi:6274496 /UG=Hs.188401 annexin A10 /FL=gb:AF196478.1 gb:NM_007193.2	
Metallothionein 1F (functional) SEQ ID NOS:31 (nucleotide) and 94 (amino acid)	Consensus includes gb:M10943 /DEF=Human metallothionein-If gene (hMT-If) /FEA=CDS /DB_XREF=gi:187540 /UG=Hs.203936 metallothionein 1F (functional)	217165_x_at
Annexin A1 SEQ ID NOS:32 (nucleotide) and 95 (amino acid)	gb:NM_000700.1 /DEF=Homo sapiens annexin A1 (ANXA1), mRNA. /FEA=mRNA /GEN=ANXA1 /PROD=annexin I /DB_XREF=gi:4502100 /UG=Hs.78225 annexin A1 /FL=gb:BC001275.1 gb:NM_000700.1	201012_at
Secretory leukocyte protease inhibitor (antileukoproteinase) SEQ ID NOS:33 (nucleotide) and 96 (amino acid)	gb:NM_003064.1 /DEF=Homo sapiens secretory leukocyte protease inhibitor (antileukoproteinase) (SLPI), mRNA. /FEA=mRNA /GEN=SLPI /PROD=secretory leukocyte protease inhibitor(antileukoproteinase) /DB_XREF=gi:4507064 /UG=Hs.251754 secretory leukocyte protease inhibitor (antileukoproteinase) /FL=gb:NM_003066.1 gb:AF114471.1 gb:NM_003064.1	203021_at
Polymeric immunoglobulin receptor SEQ ID NOS:34 (nucleotide) and 97 (amino acid)	gb:NM_002644.1 /DEF=Homo sapiens polymeric immunoglobulin receptor (PIGR), mRNA. /FEA=mRNA /GEN=PIGR /PROD=polymeric immunoglobulin receptor /DB_XREF=gi:11342673 /UG=Hs.288579 polymeric immunoglobulin receptor /FL=gb:NM_002644.1	204213_at
Carcinoembryonic antigen-related cell adhesion molecule 5 SEQ ID NOS:35 (nucleotide) and 98 (amino acid)	gb:NM_004363.1 /DEF=Homo sapiens carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), mRNA. /FEA=mRNA /GEN=CEACAM5 /PROD=carcinoembryonic antigen-related cell adhesionmolecule 5 /DB_XREF=gi:11386170 /UG=Hs.220529 carcinoembryonic antigen-related cell adhesion molecule 5 /FL=gb:NM_004363.1 gb:M29540.1	201884_at
Protein tyrosine phosphatase, receptor type, N polypeptide 2	gb:NM_002847.1 /DEF=Homo sapiens protein tyrosine phosphatase, receptor type, N polypeptide 2 (PTPRN2), mRNA.	203029_s_at

SEQ ID NOS:36 (nucleotide) and 99 (amino acid)	/FEA=mRNA /GEN=PTPRN2 /PROD=protein tyrosine phosphatase, receptor type, Npolypeptide 2 /DB_XREF=gi:11386148 /UG=Hs.74624 protein tyrosine phosphatase, receptor type, N polypeptide 2 /FL=gb:NM_002847.1 gb:U66702.1 gb:AF007555.1	
Cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7) SEQ ID NOS:37 (nucleotide) and 100 (amino acid)	gb:NM_000492.2 /DEF=Homo sapiens cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub- family C, member 7) (CFTR), mRNA. /FEA=mRNA /GEN=CFTR /PROD=cystic fibrosis transmembrane conductanceregulator, ATP-binding cassette (sub-family C, member 7) /DB_XREF=gi:6995995 /UG=Hs.663 cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub- family C, member 7) /FL=gb:NM_000492.2	205043_at
DVS27-related protein SEQ ID NOS:38 (nucleotide) and 101 (amino acid)	gb:AB024518.1 /DEF=Homo sapiens mRNA for DVS27-related protein, complete cds. /FEA=mRNA /GEN=DVS27 /PROD=DVS27-related protein /DB_XREF=gi:4520327 /UG=Hs.58589 glycogenin 2 /FL=gb:AB024518.1	209821_at
Insulin-like growth factor binding protein 2 (36kD) SEQ ID NOS:39 (nucleotide) and 102 (amino acid)	gb:NM_000597.1 /DEF=Homo sapiens insulin-like growth factor binding protein 2 (36kD) (IGFBP2), mRNA. /FEA=mRNA /GEN=IGFBP2 /PROD=insulin-like growth factor binding protein 2(36kD) /DB_XREF=gi:10835156 /UG=Hs.162 insulin-like growth factor binding protein 2 (36kD) /FL=gb:NM_000597.1 gb:BC004312.1 gb:M35410.1	202718_at
Inhibitor of DNA binding 3, dominant negative helix-loop- helix protein SEQ ID NOS:40 (nucleotide) and 103 (amino acid)	gb:NM_002167.1 /DEF=Homo sapiens inhibitor of DNA binding 3, dominant negative helix-loop-helix protein (ID3), mRNA. /FEA=mRNA /GEN=ID3 /PROD=inhibitor of DNA binding 3, dominant negativehelix-loop-helix protein /DB_XREF=gi:10835060 /UG=Hs.76884 inhibitor of DNA binding 3, dominant negative helix-loop-helix protein /FL=gb:NM_002167.1	207826_s_at
Phospholipase A2, group IIA (platelets,	Consensus includes gb:X00452.1 /DEF=Human mRNA for DC classII	203649_s_at

synovial fluid) SEQ ID NOS:41 (nucleotide) and 104 (amino acid)	histocompatibility antigen alpha-chain. /FEA=mRNA /PROD=DC classII histocompatibility antigenalpha-chain /DB_XREF=gi:32265 /UG=Hs.198253 major histocompatibility complex, class II, DQ alpha 1	
Purkinje cell protein 4 SEQ ID NOS:42 (nucleotide) and 105 (amino acid)	gb:NM_006198.1 /DEF=Homo sapiens Purkinje cell protein 4 (PCP4), mRNA. /FEA=mRNA /GEN=PCP4 /PROD=Purkinje cell protein 4 /DB_XREF=gi:5453857 /UG=Hs.80296 Purkinje cell protein 4 /FL=gb:U52969.1 gb:NM_006198.1	205549_at
G protein-coupled receptor 49 SEQ ID NOS:43 (nucleotide), 44 (nucleotide) and 106 (amino acid)	Consensus includes gb:AL524520 /FEA=EST /DB_XREF=gi:12788013 /DB_XREF=est:AL524520 /CLONE=CS0DC007YG21 (3 prime) /UG=Hs.285529 G protein-coupled receptor 49	213880_at
Fucosyltransferase 3 (galactoside 3(4)-L- fucosyltransferase, Lewis blood group included) SEQ ID NOS:45 (nucleotide), 46 (nucleotide) and 107 (amino acid)	Consensus includes gb:AW080549 /FEA=EST /DB_XREF=gi:6035701 /DB_XREF=est:xc33a08.x1 /CLONE=IMAGE:2586038 /UG=Hs.169238 fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group included)	214088_s_at
Interferon, alpha- inducible protein 27 SEQ ID NOS:47 (nucleotide) and 108 (amino acid)	gb:NM_005532.1 /DEF=Homo sapiens interferon, alpha-inducible protein 27 (IFI27), mRNA. /FEA=mRNA /GEN=IFI27 /PROD=interferon, alpha- inducible protein 27 /DB_XREF=gi:5031780 /UG=Hs.278613 interferon, alpha-inducible protein 27 /FL=gb:NM_005532.1	202411_at
Serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5 SEQ ID NOS:48 (nucleotide) and 109 (amino acid)	gb:NM_002639.1 /DEF=Homo sapiens serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5 (SERPINB5), mRNA. /FEA=mRNA /GEN=SERPINB5 /PROD=serine (or cysteine) proteinase inhibitor, cladeB (ovalbumin), member 5 /DB_XREF=gi:4505788 /UG=Hs.55279 serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5	204855_at

	/FL=gb:NM_002639.1 gb:U04313.1	
Homo sapiens CD44 isoform RC (CD44) mRNA, complete cds SEQ ID NOS:49 (nucleotide) and 110 (amino acid)	gb:AF098641.1 /DEF=Homo sapiens CD44 isoform RC (CD44) mRNA, complete cds. /FEA=mRNA /GEN=CD44 /PROD=CD44 isoform RC /DB_XREF=gi:3832517 /UG=Hs.306278 Homo sapiens CD44 isoform RC (CD44) mRNA, complete cds /FL=gb:AF098641.1	210916_s_at
Solute carrier family 7 (cationic amino acid transporter, y+ system), member 8 SEQ ID NOS:50 (nucleotide) and 111 (amino acid)	gb:NM_012244.1 /DEF=Homo sapiens solute carrier family 7 (cationic amino acid transporter, y+ system), member 8 (SLC7A8), mRNA. /FEA=mRNA /GEN=SLC7A8 /PROD=solute carrier family 7 (cationic amino acid transporter, y+ system), member 8 /DB_XREF=gi:6912669 /UG=Hs.22891 solute carrier family 7 (cationic amino acid transporter, y+ system), member 8 /FL=gb:AB037669.1 gb:AF171669.1 gb:NM_012244.1	202752_x_at
Membrane protein, palmitoylated 1 (55kD) SEQ ID NOS:51 (nucleotide) and 112 (amino acid)	gb:NM_002436.2 /DEF=Homo sapiens membrane protein, palmitoylated 1 (55kD) (MPP1), mRNA. /FEA=mRNA /GEN=MPP1 /PROD=palmitoylated membrane protein 1 /DB_XREF=gi:6006024 /UG=Hs.1861 membrane protein, palmitoylated 1 (55kD) /FL=gb:BC002392.1 gb:M64925.1 gb:NM_002436.2	202974_at
Tumor protein p53 (Li-Fraumeni syndrome) SEQ ID NOS:52 (nucleotide) and 113 (amino acid)	gb:K03199.1 /DEF=Human p53 cellular tumor antigen mRNA, complete cds. /FEA=mRNA /GEN=TP53 /DB_XREF=gi:189478 /UG=Hs.1846 tumor protein p53 (Li-Fraumeni syndrome) /FL=gb:K03199.1	211300_s_at
S100 calcium-binding protein P SEQ ID NOS:53 (nucleotide) and 114 (amino acid)	gb:NM_005980.1 /DEF=Homo sapiens S100 calcium-binding protein P (S100P), mRNA. /FEA=mRNA /GEN=S100P /PROD=S100 calcium-binding protein P /DB_XREF=gi:5174662 /UG=Hs.2962 S100 calcium-binding protein P /FL=gb:NM_005980.1	204351_at
Serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	gb:AF119873.1 /DEF=Homo sapiens PRO2275 mRNA, complete cds. /FEA=mRNA /PROD=PRO2275 /DB_XREF=gi:7770182 /UG=Hs.297681 serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase,	211429_s_at

SEQ ID NOS:54 (nucleotide) and 115 (amino acid)	antitrypsin), member 1 /FL=gb:AF119873.1	
Eukaryotic translation initiation factor 5A SEQ ID NOS:55 (nucleotide) and 116 (amino acid)	gb:NM_001970.1 /DEF=Homo sapiens eukaryotic translation initiation factor 5A (EIF5A), mRNA. /FEA=mRNA /GEN=EIF5A /PROD=eukaryotic translation initiation factor 5A /DB_XREF=gi:4503544 /UG=Hs.119140 eukaryotic translation initiation factor 5A /FL=gb:BC000751.1 gb:BC001832.1 gb:M23419.1 gb:NM_001970.1	201123_s_at
Old astrocyte specifically induced substance SEQ ID NOS:56 (nucleotide), 57 (nucleotide) and 117 (amino acid)	Consensus includes gb:AF055009.1 /DEF=Homo sapiens clone 24747 mRNA sequence. /FEA=mRNA /DB_XREF=gi:3005731 /UG=Hs.13456 Homo sapiens clone 24747 mRNA sequence	213059_at
UDP glycosyltransferase 1 family, polypeptide A3 SEQ ID NOS:58 (nucleotide) and 118 (amino acid)	gb:NM_019093.1 /DEF=Homo sapiens UDP glycosyltransferase 1 family, polypeptide A3 (UGT1A3), mRNA. /FEA=CDS /GEN=UGT1A3 /PROD=UDP glycosyltransferase 1 family, polypeptide A3 /DB_XREF=gi:13487899 /UG=Hs.326543 UDP glycosyltransferase 1 family, polypeptide A3 /FL=gb:NM_019093.1	208596_s_at
Alpha-2-HS- glycoprotein SEQ ID NOS:59 (nucleotide) and 119 (amino acid)	gb:AF130057.1 /DEF=Homo sapiens clone FLB5539 PRO1454 mRNA, complete cds. /FEA=mRNA /PROD=PRO1454 /DB_XREF=gi:11493420 /UG=Hs.323288 Homo sapiens clone FLB5539 PRO1454 mRNA, complete cds /FL=gb:AF130057.1	210929_s_at
ESTs, Highly similar to A39092 glucuronosyltransferase [H.sapiens] SEQ ID NOS:60 (nucleotide), 61 (nucleotide) and 120 (amino acid)	Consensus includes gb:AV691323 /FEA=EST /DB_XREF=gi:10293186 /DB_XREF=est:AV691323 /CLONE=GKCEWF11 /UG=Hs.2056 UDP glycosyltransferase 1 family, polypeptide A9	215125_s_at
UDP glycosyltransferase 1 family, polypeptide A1	gb:NM_000463.1 /DEF=Homo sapiens UDP glycosyltransferase 1 family, polypeptide A1 (UGT1A1), mRNA. /FEA=mRNA /GEN=UGT1A1	207126_x_at

SEQ ID NOS:62 (nucleotide) and 121 (amino acid)	/PROD=UDP glycosyltransferase 1 family, polypeptideA1 /DB_XREF=gi:8850235 /UG=Hs.278896 UDP glycosyltransferase 1 family, polypeptide A1 /FL=gb:M57899.1 gb:NM_000463.1	
Serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1 SEQ ID NOS:63 (nucleotide) and 122 (amino acid)	gb:NM_000295.1 /DEF=Homo sapiens serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1 (SERPINA1), mRNA. /FEA=mRNA /GEN=SERPINA1 /PROD=serine (or cysteine) proteinase inhibitor, cladeA (alpha-1 antiproteinase, antitrypsin), member 1 /DB_XREF=gi:4505792 /UG=Hs.297681 serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1 /FL=gb:AF130068.1 gb:M11465.1 gb:K01396.1 gb:NM_000295.1	202833_s_at
Nerve growth factor receptor (TNFRSF16) associated protein 1 SEQ ID NOS:64 (nucleotide) and 123 (amino acid)	gb:NM_014380.1 /DEF=Homo sapiens p75NTR-associated cell death executor; ovarian granulosa cell protein (13kD) (DXS6984E), mRNA. /FEA=mRNA /GEN=DXS6984E /PROD=p75NTR- associated cell death executor; ovariangranulosa cell protein (13kD) /DB_XREF=gi:7657043 /UG=Hs.17775 p75NTR-associated cell death executor; ovarian granulosa cell protein (13kD) /FL=gb:NM_014380.1 gb:AF187064.1	217963_s_at
Collagen, type XVIII, alpha 1 SEQ ID NOS:65 (nucleotide) and 124 (amino acid)	Consensus includes gb:NM_030582.1 /DEF=Homo sapiens collagen, type XVIII, alpha 1 (COL18A1), mRNA. /FEA=CDS /GEN=COL18A1 /PROD=collagen, type XVIII, alpha 1 /DB_XREF=gi:13385619 /UG=Hs.78409 collagen, type XVIII, alpha 1 /FL=gb:NM_030582.1 gb:AF018081.1 gb:AF184060.1 gb:NM_016214.1	209081_s_at
Collagen, type IX, alpha 3 SEQ ID NOS:66 (nucleotide) and 125 (amino acid)	gb:NM_001853.1 /DEF=Homo sapiens collagen, type IX, alpha 3 (COL9A3), mRNA. /FEA=mRNA /GEN=COL9A3 /PROD=collagen, type IX, alpha 3 /DB_XREF=gi:4502966 /UG=Hs.53563 collagen, type IX, alpha 3 /FL=gb:L41162.1 gb:NM_001853.1	204724_s_at

The biomarkers have expression levels in the cells that are dependent on the activity of the EGFR signal transduction pathway and that are also highly correlated with EGFR modulator sensitivity exhibited by the cells. Biomarkers serve as useful molecular tools for predicting a response to EGFR modulators, preferably biological molecules, small molecules, and the like that affect EGFR kinase activity via direct or indirect inhibition or antagonism of EGFR kinase function or activity.

EGFR MODULATORS

As used herein, the term "EGFR modulator" is intended to mean a compound or drug that is a biological molecule or a small molecule that directly or indirectly modulates EGFR activity or the EGFR signal transduction pathway. Thus, compounds or drugs as used herein is intended to include both small molecules and biological molecules. Direct or indirect modulation includes activation or inhibition of EGFR activity or the EGFR signal transduction pathway. In one aspect, inhibition refers to inhibition of the binding of EGFR to an EGFR ligand such as, for example, EGF. In another aspect, inhibition refers to inhibition of the kinase activity of EGFR.

EGFR modulators include, for example, EGFR specific ligands, small molecule EGFR inhibitors, and EGFR monoclonal antibodies. In one aspect, the EGFR modulator inhibits EGFR activity and/or inhibits the EGFR signal transduction pathway. In another aspect, the EGFR modulator is an EGFR monoclonal antibody that inhibits EGFR activity and/or inhibits the EGFR signal transduction pathway.

EGFR modulators include biological molecules or small molecules. Biological molecules include all lipids and polymers of monosaccharides, amino acids, and nucleotides having a molecular weight greater than 450. Thus, biological molecules include, for example, oligosaccharides and polysaccharides; oligopeptides, polypeptides, peptides, and proteins; and oligonucleotides and polynucleotides. Oligonucleotides and polynucleotides include, for example, DNA and RNA.

Biological molecules further include derivatives of any of the molecules described above. For example, derivatives of biological molecules include lipid and glycosylation derivatives of oligopeptides, polypeptides, peptides, and proteins.

Derivatives of biological molecules further include lipid derivatives of oligosaccharides and polysaccharides, e.g., lipopolysaccharides. Most typically,

biological molecules are antibodies, or functional equivalents of antibodies.

Functional equivalents of antibodies have binding characteristics comparable to those of antibodies, and inhibit the growth of cells that express EGFR. Such functional equivalents include, for example, chimerized, humanized, and single chain antibodies as well as fragments thereof.

Functional equivalents of antibodies also include polypeptides with amino acid sequences substantially the same as the amino acid sequence of the variable or hypervariable regions of the antibodies. An amino acid sequence that is substantially the same as another sequence, but that differs from the other sequence by means of one or more substitutions, additions, and/or deletions, is considered to be an equivalent sequence. Preferably, less than 50%, more preferably less than 25%, and still more preferably less than 10%, of the number of amino acid residues in a sequence are substituted for, added to, or deleted from the protein.

The functional equivalent of an antibody is preferably a chimerized or humanized antibody. A chimerized antibody comprises the variable region of a non-human antibody and the constant region of a human antibody. A humanized antibody comprises the hypervariable region (CDRs) of a non-human antibody. The variable region other than the hypervariable region, e.g., the framework variable region, and the constant region of a humanized antibody are those of a human antibody.

Suitable variable and hypervariable regions of non-human antibodies may be derived from antibodies produced by any non-human mammal in which monoclonal antibodies are made. Suitable examples of mammals other than humans include, for example, rabbits, rats, mice, horses, goats, or primates.

Functional equivalents further include fragments of antibodies that have binding characteristics that are the same as, or are comparable to, those of the whole antibody. Suitable fragments of the antibody include any fragment that comprises a sufficient portion of the hypervariable (i.e., complementarity determining) region to bind specifically, and with sufficient affinity, to EGFR tyrosine kinase to inhibit growth of cells that express such receptors.

Such fragments may, for example, contain one or both Fab fragments or the F(ab')₂ fragment. Preferably, the antibody fragments contain all six complementarity

determining regions of the whole antibody, although functional fragments containing fewer than all of such regions, such as three, four, or five CDRs, are also included.

In one aspect, the fragments are single chain antibodies, or Fv fragments. Single chain antibodies are polypeptides that comprise at least the variable region of the heavy chain of the antibody linked to the variable region of the light chain, with or without an interconnecting linker. Thus, Fv fragment comprises the entire antibody combining site. These chains may be produced in bacteria or in eukaryotic cells.

The antibodies and functional equivalents may be members of any class of immunoglobulins, such as IgG, IgM, IgA, IgD, or IgE, and the subclasses thereof. In one aspect, the antibodies are members of the IgG1 subclass. The functional equivalents may also be equivalents of combinations of any of the above classes and subclasses.

In one aspect, EGFR antibodies can be selected from chimerized, humanized, fully human, and single chain antibodies derived from the murine antibody 225 described in U.S. Patent No. 4,943,533 to Mendelsohn et al., including, for example, cetuximab.

In another aspect, the EGFR antibody can be selected from the antibodies described in U.S. Patent No. 6,235,883 to Jakobovits et al., U.S. Patent No. 5,558,864 to Bendi et al., and U.S. Patent No. 5,891,996 to Mateo de Acosta del Rio et al.

In addition to the biological molecules discussed above, the EGFR modulators useful in the invention may also be small molecules. Any molecule that is not a biological molecule is considered herein to be a small molecule. Some examples of small molecules include organic compounds, organometallic compounds, salts of organic and organometallic compounds, saccharides, amino acids, and nucleotides. Small molecules further include molecules that would otherwise be considered biological molecules, except their molecular weight is not greater than 450. Thus, small molecules may be lipids, oligosaccharides, oligopeptides, and oligonucleotides and their derivatives, having a molecular weight of 450 or less.

It is emphasized that small molecules can have any molecular weight. They are merely called small molecules because they typically have molecular weights less than 450. Small molecules include compounds that are found in nature as well as synthetic compounds. In one embodiment, the EGFR modulator is a small molecule

that inhibits the growth of tumor cells that express EGFR. In another embodiment, the EGFR modulator is a small molecule that inhibits the growth of refractory tumor cells that express EGFR. In yet another embodiment, the EGFR modulator is erlotinib HCl or gefitinib.

5 Numerous small molecules have been described as being useful to inhibit EGFR. For example, U.S. Patent No. 5,656,655 to Spada et al. discloses styryl substituted heteroaryl compounds that inhibit EGFR. The heteroaryl group is a monocyclic ring with one or two heteroatoms, or a bicyclic ring with 1 to about 4 heteroatoms, the compound being optionally substituted or polysubstituted.

10 U.S. Patent No. 5,646,153 to Spada et al. discloses bis mono and/or bicyclic aryl heteroaryl, carbocyclic, and heterocarbocyclic compounds that inhibit EGFR.

 U.S. Patent No. 5,679,683 to Bridges et al. discloses tricyclic pyrimidine compounds that inhibit the EGFR. The compounds are fused heterocyclic pyrimidine derivatives described at column 3, line 35 to column 5, line 6.

15 U.S. Patent No. 5,616,582 to Barker discloses quinazoline derivatives that have receptor tyrosine kinase inhibitory activity.

 Fry et al., Science 265, 1093-1095 (1994) in Figure 1 discloses a compound having a structure that inhibits EGFR.

 Osherov et al. disclose tyrphostins that inhibit EGFR/HER1 and HER 2,
20 particularly those in Tables I, II, III, and IV.

 U.S. Patent No. 5,196,446 to Levitzki et al. discloses heteroarylethenediyl or heteroarylethendeiylaryl compounds that inhibit EGFR, particularly from column 2, line 42 to column 3, line 40.

 Panek et al., Journal of Pharmacology and Experimental Therapeutics 283,
25 1433-1444 (1997) discloses a compound identified as PD166285 that inhibits the EGFR, PDGFR, and FGFR families of receptors. PD166285 is identified as 6-(2,6-dichlorophenyl)-2-(4-(2-diethylaminoethoxy)phenylamino)-8-methyl-8H-pyrido(2,3-d)pyrimidin-7-one having the structure shown in Figure 1 on page 1436.

30 BIOMARKERS AND BIOMARKER SETS

 The invention includes individual biomarkers and biomarker sets having both diagnostic and prognostic value in disease areas in which signaling through EGFR or

the EGFR pathway is of importance, e.g., in cancers or tumors, in immunological disorders, conditions or dysfunction, or in disease states in which cell signaling and/or cellular proliferation controls are abnormal or aberrant. The biomarker sets comprise a plurality of biomarkers such as, for example, a plurality of the biomarkers provided
5 in Table 1, that highly correlate with resistance or sensitivity to one or more EGFR modulators.

The biomarker sets of the invention enable one to predict or reasonably foretell the likely effect of one or more EGFR modulators in different biological systems or for cellular responses. The biomarker sets can be used in *in vitro* assays of
10 EGFR modulator response by test cells to predict *in vivo* outcome. In accordance with the invention, the various biomarker sets described herein, or the combination of these biomarker sets with other biomarkers or markers, can be used, for example, to predict how patients with cancer might respond to therapeutic intervention with one or more EGFR modulators.

15 A biomarker set of cellular gene expression patterns correlating with sensitivity or resistance of cells following exposure of the cells to one or more EGFR modulators provides a useful tool for screening one or tumor samples before treatment with the EGFR modulator. The screening allows a prediction of cells of a tumor sample exposed to one or more EGFR modulators, based on the expression results of
20 the biomarker set, as to whether or not the tumor, and hence a patient harboring the tumor, will or will not respond to treatment with the EGFR modulator.

The biomarker or biomarker set can also be used as described herein for monitoring the progress of disease treatment or therapy in those patients undergoing treatment for a disease involving an EGFR modulator.

25 The biomarkers also serve as targets for the development of therapies for disease treatment. Such targets may be particularly applicable to treatment of colon disease, such as colon cancers or tumors. Indeed, because these biomarkers are differentially expressed in sensitive and resistant cells, their expression patterns are correlated with relative intrinsic sensitivity of cells to treatment with EGFR
30 modulators. Accordingly, the biomarkers highly expressed in resistant cells may serve as targets for the development of new therapies for the tumors which are resistant to EGFR modulators, particularly EGFR inhibitors.

MICROARRAYS

The invention also includes specialized microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, comprising one or more biomarkers, showing
5 expression profiles that correlate with either sensitivity or resistance to one or more EGFR modulators. Such microarrays can be employed in *in vitro* assays for assessing the expression level of the biomarkers in the test cells from tumor biopsies, and determining whether these test cells are likely to be resistant or sensitive to EGFR modulators. For example, a specialized microarray can be prepared using all the
10 biomarkers, or subsets thereof, as described herein and shown in Table 1. Cells from a tissue or organ biopsy can be isolated and exposed to one or more of the EGFR modulators. Following application of nucleic acids isolated from both untreated and treated cells to one or more of the specialized microarrays, the pattern of gene expression of the tested cells can be determined and compared with that of the
15 biomarker pattern from the control panel of cells used to create the biomarker set on the microarray. Based upon the gene expression pattern results from the cells that underwent testing, it can be determined if the cells show a resistant or a sensitive profile of gene expression. Whether or not the tested cells from a tissue or organ biopsy will respond to one or more of the EGFR modulators and the course of
20 treatment or therapy can then be determined or evaluated based on the information gleaned from the results of the specialized microarray analysis.

ANTIBODIES

The invention also includes antibodies, including polyclonal or monoclonal,
25 directed against one or more of the polypeptide biomarkers. Such antibodies can be used in a variety of ways, for example, to purify, detect, and target the biomarkers of the invention, including both *in vitro* and *in vivo* diagnostic, detection, screening, and/or therapeutic methods.

30 KITS

The invention also includes kits for determining or predicting whether a patient would be susceptible or resistant to a treatment that comprises one or more

EGFR modulators. The patient may have a cancer or tumor such as, for example, a colon cancer or tumor. Such kits would be useful in a clinical setting for use in testing a patient's biopsied tumor or cancer samples, for example, to determine or predict if the patient's tumor or cancer will be resistant or sensitive to a given treatment or therapy with an EGFR modulator. The kit comprises a suitable container that comprises: one or more microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, that comprise those biomarkers that correlate with resistance and sensitivity to EGFR modulators, particularly EGFR inhibitors; one or more EGFR modulators for use in testing cells from patient tissue specimens or patient samples; and instructions for use. In addition, kits contemplated by the invention can further include, for example, reagents or materials for monitoring the expression of biomarkers of the invention at the level of mRNA or protein, using other techniques and systems practiced in the art such as, for example, RT-PCR assays, which employ primers designed on the basis of one or more of the biomarkers described herein, immunoassays, such as enzyme linked immunosorbent assays (ELISAs), immunoblotting, e.g., Western blots, or *in situ* hybridization, and the like, as further described herein.

APPLICATION OF BIOMARKERS AND BIOMARKER SETS

The biomarkers and biomarker sets may be used in different applications. Biomarker sets can be built from any combination of biomarkers listed in Table 1 to make predictions about the likely effect of any EGFR modulator in different biological systems. The various biomarkers and biomarkers sets described herein can be used, for example, as diagnostic or prognostic indicators in disease management, to predict how patients with cancer might respond to therapeutic intervention with compounds that modulate the EGFR, and to predict how patients might respond to therapeutic intervention that modulates signaling through the entire EGFR regulatory pathway.

While the data described herein were generated in cell lines that are routinely used to screen and identify compounds that have potential utility for cancer therapy, the biomarkers have both diagnostic and prognostic value in other diseases areas in which signaling through EGFR or the EGFR pathway is of importance, e.g., in

immunology, or in cancers or tumors in which cell signaling and/or proliferation controls have gone awry.

In accordance with the invention, cells from a patient tissue sample, e.g., a tumor or cancer biopsy, can be assayed to determine the expression pattern of one or more biomarkers prior to treatment with one or more EGFR modulators. Success or failure of a treatment can be determined based on the biomarker expression pattern of the cells from the test tissue (test cells), e.g., tumor or cancer biopsy, as being relatively similar or different from the expression pattern of a control set of the one or more biomarkers. Thus, if the test cells show a biomarker expression profile which corresponds to that of the biomarkers in the control panel of cells which are sensitive to the EGFR modulator, it is highly likely or predicted that the individual's cancer or tumor will respond favorably to treatment with the EGFR modulator. By contrast, if the test cells show a biomarker expression pattern corresponding to that of the biomarkers of the control panel of cells which are resistant to the EGFR modulator, it is highly likely or predicted that the individual's cancer or tumor will not respond to treatment with the EGFR modulator.

The invention also provides a method of monitoring the treatment of a patient having a disease treatable by one or more EGFR modulators. The isolated test cells from the patient's tissue sample, e.g., a tumor biopsy or tumor sample, can be assayed to determine the expression pattern of one or more biomarkers before and after exposure to an EGFR modulator wherein, preferably, the EGFR modulator is an EGFR inhibitor. The resulting biomarker expression profile of the test cells before and after treatment is compared with that of one or more biomarkers as described and shown herein to be highly expressed in the control panel of cells that are either resistant or sensitive to an EGFR modulator. Thus, if a patient's response is sensitive to treatment by an EGFR modulator, based on correlation of the expression profile of the one or biomarkers, the patient's treatment prognosis can be qualified as favorable and treatment can continue. Also, if, after treatment with an EGFR modulator, the test cells don't show a change in the biomarker expression profile corresponding to the control panel of cells that are sensitive to the EGFR modulator, it can serve as an indicator that the current treatment should be modified, changed, or even discontinued. This monitoring process can indicate success or failure of a patient's

treatment with an EGFR modulator and such monitoring processes can be repeated as necessary or desired.

The biomarkers of the invention can be used to predict an outcome prior to having any knowledge about a biological system. Essentially, a biomarker can be considered to be a statistical tool. Biomarkers are useful primarily in predicting the phenotype that is used to classify the biological system. In an embodiment of the invention, the goal of the prediction is to classify cancer cells as having an active or inactive EGFR pathway. Cancer cells with an inactive EGFR pathway can be considered resistant to treatment with an EGFR modulator. An inactive EGFR pathway is defined herein as a non-significant expression of the EGFR or by a classification as "resistant" or "sensitive" based on the IC₅₀ value of each colon cell line to EGFR inhibitor compound as exemplified herein.

However, although the complete function of all of the biomarkers are not currently known, some of the biomarkers are likely to be directly or indirectly involved in the EGFR signaling pathway. In addition, some of the biomarkers may function in the metabolic or other resistance pathways specific to the EGFR modulators tested. Notwithstanding, knowledge about the function of the biomarkers is not a requisite for determining the accuracy of a biomarker according to the practice of the invention.

20

EXAMPLES:

EXAMPLE 1 - Identification of Biomarkers

The biomarkers of Table 1 were identified as follows.

25 Colon Tumors and Patients:

Forty colon tumors collected from the University of London between 1998 and 2002. The median age of the patients was 70 years (range: 26-91 years). The patients were diagnosed as follows: 6 patients were designated as Duke's A, 14 as Duke's B, and 20 as Duke's C. None of the patients were treated pre-operatively, and 13 were treated post-operatively.

30

Determination of Relative Drug Sensitivity in Colon Cancer Cell Lines:

The cell line filtering process used is illustrated in FIG. 2.

The colon cancer cell lines were grown using standard cell culture conditions: RPMI 1640 supplemented to contain 10% fetal bovine serum, 100 IU/ml penicillin, 100 mg/ml streptomycin, 2 mM L-glutamine and 10 mM Hepes (all from GibcoBRL, Rockville, MD). Twenty-one colon cancer cell lines were examined for their relative sensitivity to a pair of small molecule EGFR inhibitors, erlotinib HCl and gefitinib. Cytotoxicity was assessed in cells by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay (T.L. Riss et al., 1992, Mol. Biol. Cell, 3 (Suppl.):184a). To carry out the assays, the colon cancer cells were plated at 4,000 cells/well in 96 well microtiter plates and 24 hours later serial diluted drugs were added. The concentration range for the EGFR inhibitor compounds used in the cytotoxicity assays was 50 ug/ml to 0.0016 ug/ml (roughly 100 uM to 0.0032 uM). The cells were incubated at 37 °C for 72 hours at which time the tetrazolium dye MTS (333 ug/ml final concentration in combination with the electron coupling agent phenazine methosulfate) was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light at 492 nm that can be quantified spectrophotometrically. The greater the absorbency, the greater the number of live cells. The results, provided below in Table 2 and FIG. 3, are expressed as an IC₅₀, which is the drug concentration required to inhibit cell proliferation to 50% of that of untreated cells.

Table 2 - Colon Cell Lines

Cell Line	ATCC No.	Avg. IC ₅₀
CaCo2	HTB-37	5.4
Colo 201	CCL-224	10+
Colo 205	CCL-222	10+
CS-1		10+
Difi		1
DLD-1		20
Geo		3.6
HCT116	CCL-247	67+
HCT116S542		53

HCT-8	CCL-244	10+
HT-29	HTB-38	10+
Lovo	CCL-229LS174T	3
LS1034		68+
RKORM13		29
SW1116		20
SW403		6.2
SW480	CCL-228	10+
SW837	CCL-235	7
SW948		73+
T84	CCL-248	10+
WiDr		67+

Resistance/sensitivity classification:

Two separate analyses were performed using different cut-offs to define EGFR-inhibitor resistance. For the first (designated "6-15"), the 6 cell lines with an IC₅₀ at or below 7 μ M were defined as sensitive and the remaining 15 cell lines were defined as resistant. For the second (designated "3-18"), the 3 cell lines with an IC₅₀ below 4 μ M were defined as sensitive and the remaining 18 cell lines were defined as resistant.

10 Gene Expression Profiling:

RNA was isolated from 50-70% confluent cell lines or colon cancer tumor tissue using the Rneasy kits from Qiagen (Valencia, CA). The quality of RNA was checked by measuring the 28S:18S ribosomal RNA ratio using an Agilent 2100 bioanalyzer (Agilent Technologies, Rockville, MD). Concentration of total RNA was determined spectrophotometrically. 10 μ g of total RNA was used to prepare biotinylated probes according to the Affymetrix Genechip Expression Analysis Technical Manual. Targets were hybridized to human HG-U133A gene chips according to the manufacturers instructions. Data were preprocessed using the MAS 5.0 software (Affymetrix, Santa Clara, CA). The trimmed mean intensity for each chip was scaled to 1,500 to account for minor differences in global chip intensity so

that the overall expression level for each sample is comparable.

Data Analysis

All 22,215 probes (gene sequences) present on the U133A chip were considered as potential predictive biomarkers. To restrict the analysis to gene sequences expressed at a moderate level in colon tumor(s), gene sequences without at least one expression value of 2X the mean value for the array (3000 expression units) were removed leaving 6988 gene sequences. Next, to identify genes with variable expression in colon tumors (and therefore more likely to be able to correlate with variability in response to treatment), gene sequences with a VARP value (using log₁₀-transformed data) < 0.1 were removed leaving 745 gene sequences. Next, the same expression and variance filters were applied to the remaining 745 gene sequences using the colon cell line data, reducing to 332 gene sequences for analysis (FIG. 1).

The 332 gene sequences were then subjected to a two-sided T-test using the Resistance/sensitivity classifications of the cell lines described above (FIG. 3). A total of 12 gene sequences had a p-value of <0.05 for both analyses (T-test Results I, FIG. 4). For the "6-15" analysis, 19 gene sequences were found to have a p-value <0.05 (T-Test Results II, FIG. 5). For the "3-18" analysis, 29 gene sequences were found to have a p-value <0.05 (T-test Results III, FIG. 6). Table 1 provides the biomarkers identified using the two-sided T-test.

EXAMPLE 2 - Untreated Xenograph Profiles

In Example 1, biomarkers were identified using sensitivity resistance profiles of cell lines to gefitinib and erlotinib HCl. The present example provided efficacy data for cetuximab (C225) in the colon cancer xenograft models Geo (sensitive to C225) and HT29 (resistant to C225).

In Vivo Antitumor Testing

Tumors were propagated in nude mice as subcutaneous (sc) transplants using tumor fragments obtained from donor mice. Tumor passage occurred approximately every two to four weeks. Tumors were then allowed to grow to the pre-determined

size window (usually between 100-200 mg, tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Animals were treated with C225 (1 mg/mouse q3d X 10, 14, ip). Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provided a measure of treatment-related toxicity. Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reached a predetermined target size of 1 gm or became necrotic. Tumor weights (mg) were estimated from the formula:

$$\text{Tumor weight} = (\text{length} \times \text{width}^2)/2$$

Antitumor activity was determined in terms of primary tumor growth inhibition. This was determined in two ways: (i) calculating the relative median tumor weight (MTW) of treated (T) and control (C) mice at various time points (effects were expressed as %T/C); and (ii) calculating the tumor growth delay (T-C value), defined as the difference in time (days) required for the treated tumors (T) to reach a predetermined target size compared to those of the control group (C). Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test for comparisons of time to reach tumor target size (Gehan 1965). Statistical significance was declared at $p < 0.05$. Antitumor activity was defined as a continuous MTW %T/C $\leq 50\%$ for at least 1 tumor volume doubling time (TVDT) any time after the start of treatment, where TVDT (tumor volume doubling time) = median time (days) for control tumors to reach target size – median time (days) for control tumors to reach half the target size. In addition, treatment groups had to be accompanied by a statistically significant tumor growth delay (T-C value) ($p < 0.05$) to be termed active.

Treated animals were checked daily for treatment related toxicity/mortality. When death occurred, the day of death was recorded. Treated mice dying prior to having their tumors reach target size were considered to have died from drug toxicity. No control mice died bearing tumors less than target size. Treatment groups with more than one death caused by drug toxicity were considered to have had excessively toxic treatments and their data were not included in the evaluation of the compound's antitumor efficacy.

Table 3 provides the resulting untreated xenograph profiles.

Table 3 - Untreated Xenograph Profiles

Biomarker	Probe	Differential expression in Geo (sensitive) and HT-29 (resistant) untreated xenografts	Absence and Presence of HT-29 and Geo
transforming growth factor, beta-induced, 68kD	201506_at	Higher 373X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
carcinoembryonic antigen-related cell adhesion molecule 5	201884_at	Higher 85X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
nerve growth factor receptor (TNFRSF16) associated protein 1	217963_s_at	Higher 50X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)	211657_at	Higher 23X in Geo than HT-29(Absent)	HT-29 Absent Geo Present
annexin A1	201012_at	Higher 16X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
tumor protein p53 (Li-Fraumeni syndrome)	211300_s_at	Higher 11X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
DVS27-related protein	209821_at	Higher 9X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7)	205043_at	Higher 7X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	211429_s_at	Higher 7X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
bone morphogenetic protein 7 (osteogenic protein 1)	209591_s_at	Higher 4X in Geo than HT-29 (Absent)	HT-29 Absent Geo Present
interferon-stimulated protein, 15 kDa	205483_s_at	Higher 3X in Geo than HT-29(Absent)	HT-29 Absent Geo Present
S100 calcium-binding protein P	204351_at	Higher 11X in Geo than HT-29	HT-29 Present Geo Present
carcinoembryonic	203757_s_at	Higher 8X in Geo than HT-	HT-29 Present

antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)		29	Geo Present
putative integral membrane transporter	208029_s_at	Higher 7X in Geo than HT-29	HT-29 Present Geo Present
cadherin 17, LI cadherin (liver-intestine)	209847_at	Higher 4X in Geo than HT-29	HT-29 Present Geo Present
FXD domain-containing ion transport regulator 3	202489_s_at	Higher 3X in Geo than HT-29	HT-29 Present Geo Present
insulin-like growth factor binding protein 2 (36kD)	202718_at	Higher 3X in Geo than HT-29	HT-29 Present Geo Present
eukaryotic translation initiation factor 5A	201123_s_at	Higher 3X in Geo than HT-29	HT-29 Present Geo Present
3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2 (mitochondrial)	204607_at	Higher 2X in Geo than HT-29	HT-29 Present Geo Present
serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	202833_s_at	Higher 21X in HT-29 than Geo	HT-29 Present Geo Present
transmembrane protease, serine 2	211689_s_at	Higher 7X in HT-29 than Geo	HT-29 Present Geo Present
protease inhibitor 3, skin-derived (SKALP)	41469_at	Higher 6X in HT-29 than Geo	HT-29 Present Geo Present
serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5	204855_at	Higher 4X in HT-29 than Geo	HT-29 Present Geo Present
fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	204379_s_at	Higher 3X in HT-29 than Geo	HT-29 Present Geo Present
mucin 3B	214898_x_at	Higher 3X in HT-29 than Geo	HT-29 Present Geo Present
fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group included)	214088_s_at	Higher 3X in HT-29 than Geo	HT-29 Present Geo Present
phospholipase A2, group IIA (platelets,	203649_s_at	Higher 2X in HT-29 than Geo	HT-29 Present Geo Present

synovial fluid)			
A kinase (PRKA) anchor protein (gravin) 12	210517_s_at	Higher 339X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	202628_s_at	Higher 280X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
ESTs, Highly similar to A39092 glucuronosyltransferase [H.sapiens]	215125_s_at	Higher 75X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
Purkinje cell protein 4	205549_at	Higher 38X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
lectin, galactoside-binding, soluble, 1 (galectin 1)	201105_at	Higher 33X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
old astrocyte specifically induced substance	213059_at	Higher 29X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
UDP glycosyltransferase 1 family, polypeptide A3	208596_s_at	Higher 23X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
hypothetical protein PP1665	213343_s_at	Higher 21X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
membrane protein, palmitoylated 1 (55kD)	202974_at	Higher 9X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
caudal type homeo box transcription factor 2	206387_at	Higher 8X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
polymeric immunoglobulin receptor	204213_at	Higher 7X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
mucin 5, subtypes A and C, tracheobronchial/gastric	214385_s_at	Higher 6X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
metallothionein 1G	204745_x_at	Higher 2X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
inhibitor of DNA binding 3, dominant negative helix-loop-helix protein	207826_s_at	Higher 2X in HT-29 than Geo (Absent)	HT-29 Present Geo Absent
lymphocyte antigen 75	205668_at	not differentially expressed	HT-29 Present

			Geo Absent
secretory leukocyte protease inhibitor (antileukoproteinase)	203021_at	not differentially expressed	HT-29 Present Geo Absent
dopa decarboxylase (aromatic L-amino acid decarboxylase)	205311_at	not differentially expressed	HT-29 Present Geo Absent
G protein-coupled receptor 49	213880_at	not differentially expressed	HT-29 Present Geo Absent
interferon, alpha-inducible protein 27	202411_at	not differentially expressed	HT-29 Present Geo Absent
Homo sapiens CD44 isoform RC (CD44) mRNA, complete cds	210916_s_at	not differentially expressed	HT-29 Present Geo Absent
mucin 5, subtypes A and C, tracheobronchial/gastric	214303_x_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
UDP glycosyltransferase 1 family, polypeptide A1	207126_x_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
metallothionein 1F (functional)	217165_x_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
GRO3 oncogene	207850_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
protease inhibitor 3, skin-derived (SKALP)	203691_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
annexin A10	210143_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
protein tyrosine phosphatase, receptor type, N polypeptide 2	203029_s_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	202752_x_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
collagen, type XVIII, alpha 1	209081_s_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
collagen, type IX, alpha 3	204724_s_at	absent in HT-29 and Geo	HT-29 Absent Geo Absent
alpha-2-HS-glycoprotein	210929_s_at	?	HT-29 Absent Geo Absent
metallothionein 1X	208581_x_at	?	HT-29 Absent Geo Absent
tumor necrosis factor receptor superfamily,	206467_x_at	?	HT-29 Absent Geo Absent

member 6b, decoy			
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EXAMPLE 3 - PRODUCTION OF ANTIBODIES AGAINST THE BIOMARKERS

Antibodies against the biomarkers can be prepared by a variety of methods.

5 For example, cells expressing an biomarker polypeptide can be administered to an animal to induce the production of sera containing polyclonal antibodies directed to the expressed polypeptides. In one aspect, the biomarker protein is prepared and isolated or otherwise purified to render it substantially free of natural contaminants, using techniques commonly practiced in the art. Such a preparation is then introduced
10 into an animal in order to produce polyclonal antisera of greater specific activity for the expressed and isolated polypeptide.

In one aspect, the antibodies of the invention are monoclonal antibodies (or protein binding fragments thereof). Cells expressing the biomarker polypeptide can be cultured in any suitable tissue culture medium, however, it is preferable to culture
15 cells in Earle's modified Eagle's medium supplemented to contain 10% fetal bovine serum (inactivated at about 56 °C), and supplemented to contain about 10 g/l nonessential amino acids, about 1,00 U/ml penicillin, and about 100 µg/ml streptomycin.

The splenocytes of immunized (and boosted) mice can be extracted and fused
20 with a suitable myeloma cell line. Any suitable myeloma cell line can be employed in accordance with the invention, however, it is preferable to employ the parent myeloma cell line (SP2/0), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (1981, *Gastroenterology*, 80:225-232).
25 The hybridoma cells obtained through such a selection are then assayed to identify those cell clones that secrete antibodies capable of binding to the polypeptide immunogen, or a portion thereof.

Alternatively, additional antibodies capable of binding to the biomarker polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies.
30 Such a method makes use of the fact that antibodies are themselves antigens and, therefore, it is possible to obtain an antibody that binds to a second antibody. In accordance with this method, protein specific antibodies can be used to immunize an

animal, preferably a mouse. The splenocytes of such an immunized animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones that produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic
5 antibodies to the protein-specific antibody and can be used to immunize an animal to induce the formation of further protein-specific antibodies.

EXAMPLE 4 - IMMUNOFLUORESCENCE ASSAYS .

The following immunofluorescence protocol may be used, for example, to
10 verify EGFR biomarker protein expression on cells or, for example, to check for the presence of one or more antibodies that bind EGFR biomarkers expressed on the surface of cells. Briefly, Lab-Tek II chamber slides are coated overnight at 4 °C with 10 micrograms/milliliter ($\mu\text{g/ml}$) of bovine collagen Type II in DPBS containing calcium and magnesium (DPBS++). The slides are then washed twice with cold
15 DPBS++ and seeded with 8000 CHO-CCR5 or CHO pC4 transfected cells in a total volume of 125 μl and incubated at 37 °C in the presence of 95% oxygen / 5% carbon dioxide.

The culture medium is gently removed by aspiration and the adherent cells are washed twice with DPBS++ at ambient temperature. The slides are blocked with
20 DPBS++ containing 0.2% BSA (blocker) at 0-4 °C for one hour. The blocking solution is gently removed by aspiration, and 125 μl of antibody containing solution (an antibody containing solution may be, for example, a hybridoma culture supernatant which is usually used undiluted, or serum/plasma which is usually diluted, e.g., a dilution of about 1/100 dilution). The slides are incubated for 1 hour at
25 0-4 °C. Antibody solutions are then gently removed by aspiration and the cells are washed five times with 400 μl of ice cold blocking solution. Next, 125 μl of 1 $\mu\text{g/ml}$ rhodamine labeled secondary antibody (e.g., anti-human IgG) in blocker solution is added to the cells. Again, cells are incubated for 1 hour at 0-4 °C.

The secondary antibody solution is then gently removed by aspiration and the
30 cells are washed three times with 400 μl of ice cold blocking solution, and five times with cold DPBS++. The cells are then fixed with 125 μl of 3.7% formaldehyde in DPBS++ for 15 minutes at ambient temperature. Thereafter, the cells are washed five

times with 400 μ l of DPBS++ at ambient temperature. Finally, the cells are mounted in 50% aqueous glycerol and viewed in a fluorescence microscope using rhodamine filters.

CLAIMS:

What is claimed is:

1. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the
5 method comprises:
 - (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 1;
 - (b) exposing the mammal to the EGFR modulator;
 - (c) following the exposing of step (b), measuring in the mammal the level of
10 the at least one biomarker,
wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.
2. The method of claim 1 wherein the method is an in vitro method, and
15 wherein the at least one biomarker is measured in at least one mammalian biological sample from the mammal.
3. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises:
20 (a) exposing the mammal to the EGFR modulator;
(b) following the exposing of step (a), measuring in the mammal the level of the at least one biomarker selected from the biomarkers of Table 1,
wherein a difference in the level of the at least one biomarker measured in step
(b), compared to the level of the biomarker in a mammal that has not been exposed to
25 said EGFR modulator, indicates that the mammal will respond therapeutically to said method of treating cancer.

FIG. 1 - Gene Filtering Process

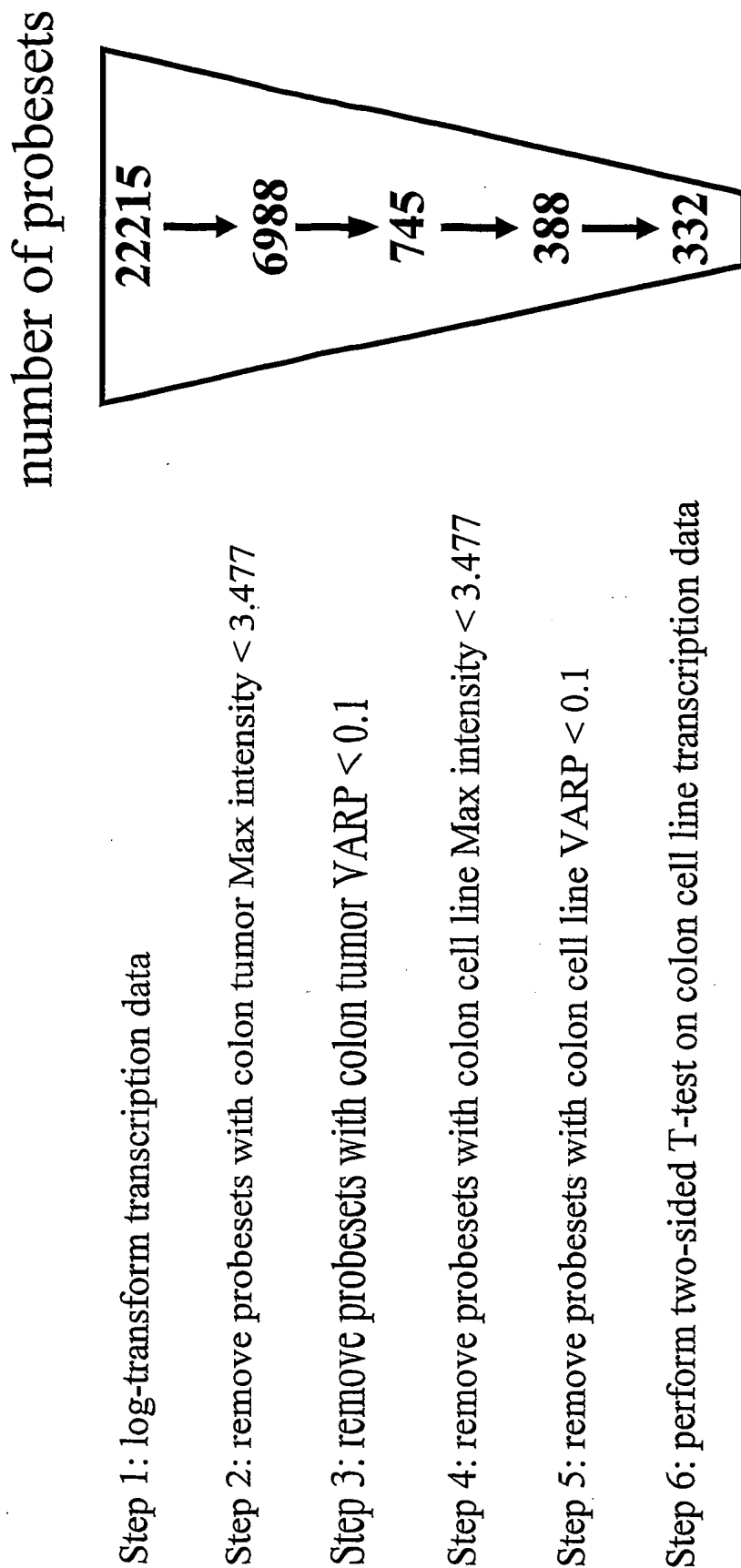


FIG. 2 - Cell Line Filtering Process

Step 1: remove EGFR-negative cell lines

Step 2: remove cell lines with variable response to EGFR inhibitors

Step 3: calculate average IC50 value for erlotinib HCl and gefitinib

number of cell lines

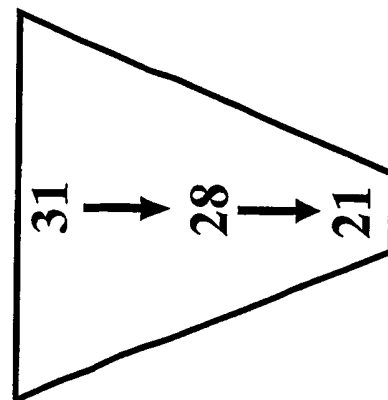


FIG. 3 - Cell Line IC50 data

Sensitive Resistant

Cell Line	Avg. IC50 (erlotinib HCl/gefitinib)
Difi	1.0 ()
Lovo	3.0 (2.4/3.6)
Geo	3.6 (3.3/4.2)
CaCo2	5.4 (5.5/5.2)
SW403	6.2 (5.7/6.8)
SW837	7.0 (7.2/6.8)

Cell Line	Avg IC50 (erlotinib HCl/gefitinib)
Colo 201	10+ (10+/10+)
Colo 205	10+ (10+/10+)
CX-1	10+ (10+/10+)
HCT-8	10+ (10+/10+)
HT-29	10+ (10+/10+)
SW480	10+ (10+/10+)
T84	10+ (10+/10+)
DLD-1	20 (20/20)
SW1116	20 (23/17)
RKORM13	29 (42/16)
HCT116S542	53 (85/20)
HCT116	67+ (116+/18)
WiDr	67+ (116+/18)
LS1034	68+ (116+/19)
SW948	73+ (116+/29)

Compare

- IC50 < 7 μ M vs. > 10 μ M (6 sensitive vs. 15 resistant)
 - IC50 < 4 μ M vs. > 5 μ M (3 sensitive vs. 18 resistant*)
- (*18 resistant is bottom 3 sensitive (CaCo2, SW403, SW837) and 15 resistant)

FIG. 4 - T-test Results I

Gene	T-test 6-15	T-test 3-18
cadherin 17, LI cadherin (liver-intestine)	0.0004	0.0010
CEACAM6	0.0004	0.0008
CEACAM6	0.0015	0.0014
lectin, galactoside-binding, soluble, 1 (galectin 1)	0.0019	0.0017
transmembrane protease, serine 2	0.0090	0.0087
mucin 5, subtypes A and C, tracheobronchial/gastric	0.0166	0.0298
HMGCoA synthase 2 (mitochondrial)	0.0169	0.0005
interferon-stimulated protein, 15 kDa	0.0204	0.0493
dopa decarboxylase	0.0235	0.0035
SERPIN E1	0.0271	0.0313
FXYD domain-containing ion transport regulator 3	0.0271	0.0156
putative integral membrane transporter	0.0439	0.0216

12 Genes with $p < 0.05$ for both comparisons

FIG. 5 - T-test Results II

Gene	T-test 6-15	T-test 3-18
protease inhibitor 3, skin-derived (SKALP)	0.0011	0.1158
caudal type homeo box transcription factor 2	0.0024	0.0573
fibroblast growth factor receptor 3	0.0118	0.0784
hypothetical protein PP1665	0.0141	0.2068
protease inhibitor 3, skin-derived (SKALP)	0.0170	0.2217
A kinase (PRKA) anchor protein (gravin) 12	0.0217	0.0907
lymphocyte antigen 75	0.0234	0.1534
mucin 5, subtypes A and C, tracheobronchial/gastric	0.0250	0.0883
metallothionein 1G	0.0337	0.3549
tumor necrosis factor receptor superfamily, member 6b, decoy	0.0357	0.0931
mucin 3B	0.0384	0.3571
metallothionein 1X	0.0411	0.4250
GRO3 oncogene	0.0413	0.0913
transforming growth factor, beta-induced, 68kD	0.0420	0.3868
bone morphogenetic protein 7 (osteogenic protein 1)	0.0435	0.1995
annexin A10	0.0437	0.1566
metallothionein 1F (functional)	0.0468	0.2643
annexin A1	0.0494	0.5338
secretory leukocyte protease inhibitor	0.0496	0.2271

19 Genes with $p < 0.05$ for 6 Sensitive vs. 15 Resistant

FIG. 6 - T-test Results III

Gene	T-test 6-15	T-test 3-18
polymeric immunoglobulin receptor	0.0535	0.0026
CEACAM 5	0.0609	0.0088
PTP, receptor type, N polypeptide 2	0.0616	0.0106
CFTR, ATP-binding cassette (sub-family C, member 7)	0.0715	0.0027
DVS27-related protein	0.1179	0.0000
insulin-like growth factor binding protein 2 (36kD)	0.2513	0.0081
inhibitor of DNA binding 3	0.2622	0.0112
phospholipase A2, group IIA (platelets, synovial fluid)	0.3361	0.0277
Purkinje cell protein 4	0.4373	0.0000
G protein-coupled receptor 49	0.4415	0.0251
fucosyltransferase 3	0.4451	0.0261
interferon, alpha-inducible protein 27	0.4453	0.0103
SERPIN B5	0.4528	0.0184
Homo sapiens CD44 isoform RC	0.4653	0.0339
solute carrier family 7, member 8	0.4748	0.0309
membrane protein, palmitoylated 1 (55kD)	0.4756	0.0248
tumor protein p53 (Li-Fraumeni syndrome)	0.5178	0.0258
S100 calcium-binding protein P	0.5498	0.0423
SERPIN A1	0.5579	0.0200
eukaryotic translation initiation factor 5A	0.5974	0.0083
old astrocyte specifically induced substance	0.6224	0.0325
UDP glycosyltransferase 1 family, polypeptide A3	0.6251	0.0008
alpha-2-HS-glycoprotein	0.6449	0.0131
ESTs, Highly similar to A39092 glucuronosyltransferase	0.6587	0.0017
UDP glycosyltransferase 1 family, polypeptide A1	0.7178	0.0010
SERPIN A1	0.7266	0.0205
nerve growth factor receptor associated protein 1	0.8525	0.0033
collagen, type XVIII, alpha 1	0.9341	0.0020
collagen, type IX, alpha 3	0.9861	0.0007

29 Genes with $p < 0.05$ for 3 Sensitive vs. 18 Resistant

SEQUENCE LISTING

<110> Clark, Edwin
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 Yoganathan, Suganthy
 Jackson, Donald

<120> BIOMARKERS AND METHODS FOR DETERMINING SENSITIVITY TO EPIDERMAL
 GROWTH FACTOR RECEPTOR MODULATORS

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<150> US 60/535,151

<151> 2004-01-07

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<211> 454

<212> DNA

<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<211> 1448
<212> DNA
<213> Homo sapiens

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<210> 30
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<212> DNA
<213> Homo sapiens

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 <211> 1935
 <212> DNA
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 <211> 1408
 <212> DNA
 <213> Homo sapiens

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<210> 33
<211> 399
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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1952

<210> 52

<211> 1760

<212> DNA

<213> Homo sapiens

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 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<211> 1821

<212> DNA

<213> Homo sapiens

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<210> 57
<211> 2370
<212> DNA
<213> Homo sapiens

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<210> 58

<211> 1605

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<213> Homo sapiens

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 <213> Homo sapiens

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 <213> Homo sapiens

<400> 66
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<210> 67
 <211> 832
 <212> PRT
 <213> Homo sapiens

<400> 67

Met Ile Leu Gln Ala His Leu His Ser Leu Cys Leu Leu Met Leu Tyr
 1 5 10 15

Leu Ala Thr Gly Tyr Gly Gln Glu Gly Lys Phe Ser Gly Pro Leu Lys
 20 25 30

Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile
 35 40 45

Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly
 50 55 60

Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Glu Gly Leu Leu Tyr Tyr
 65 70 75 80

Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val
 85 90 95

Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile
 100 105 110

Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln
 115 120 125

Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro
 130 135 140

Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn
 145 150 155 160

Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn
 165 170 175

Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr
 180 185 190

Arg Glu Gly Ser Gln Glu Leu Asn Pro Ala Lys Asn Pro Ser Tyr Asn
 195 200 205

Leu Val Ile Ser Val Lys Asp Met Gly Gly Gln Ser Glu Asn Ser Phe
 210 215 220

Ser Asp Thr Thr Ser Val Asp Ile Ile Val Thr Glu Asn Ile Trp Lys
 225 230 235 240

Ala Pro Lys Pro Val Glu Met Val Glu Asn Ser Thr Asp Pro His Pro
 245 250 255

Ile Lys Ile Thr Gln Val Arg Trp Asn Asp Pro Gly Ala Gln Tyr Ser
 260 265 270

Leu Val Asp Lys Glu Lys Leu Pro Arg Phe Pro Phe Ser Ile Asp Gln
 275 280 285

Glu Gly Asp Ile Tyr Val Thr Gln Pro Leu Asp Arg Glu Glu Lys Asp
 290 295 300

Ala Tyr Val Phe Tyr Ala Val Ala Lys Asp Glu Tyr Gly Lys Pro Leu
 305 310 315 320

Ser Tyr Pro Leu Glu Ile His Val Lys Val Lys Asp Ile Asn Asp Asn
 325 330 335

Pro Pro Thr Cys Pro Ser Pro Val Thr Val Phe Glu Val Gln Glu Asn
 340 345 350

Glu Arg Leu Gly Asn Ser Ile Gly Thr Leu Thr Ala His Asp Arg Asp
 355 360 365

Glu Glu Asn Thr Ala Asn Ser Phe Leu Asn Tyr Arg Ile Val Glu Gln
 370 375 380

Thr Pro Lys Leu Pro Met Asp Gly Leu Phe Leu Ile Gln Thr Tyr Ala
 385 390 395 400

Gly Met Leu Gln Leu Ala Lys Gln Ser Leu Lys Lys Gln Asp Thr Pro
 405 410 415

Gln Tyr Asn Leu Thr Ile Glu Val Ser Asp Lys Asp Phe Lys Thr Leu
 420 425 430

Cys Phe Val Gln Ile Asn Val Ile Asp Ile Asn Asp Gln Ile Pro Ile
 435 440 445

Phe Glu Lys Ser Asp Tyr Gly Asn Leu Thr Leu Ala Glu Asp Thr Asn
 450 455 460

Ile Gly Ser Thr Ile Leu Thr Ile Gln Ala Thr Asp Ala Asp Glu Pro
 465 470 475 480

Phe Thr Gly Ser Ser Lys Ile Leu Tyr His Ile Ile Lys Gly Asp Ser
 485 490 495

Glu Gly Arg Leu Gly Val Asp Thr Asp Pro His Thr Asn Thr Gly Tyr
 500 505 510

Val Ile Ile Lys Lys Pro Leu Asp Phe Glu Thr Ala Ala Val Ser Asn
 515 520 525

Ile Val Phe Lys Ala Glu Asn Pro Glu Pro Leu Val Phe Gly Val Lys
 530 535 540

Tyr Asn Ala Ser Ser Phe Ala Lys Phe Thr Leu Ile Val Thr Asp Val
 545 550 555 560

Asn Glu Ala Pro Gln Phe Ser Gln His Val Phe Gln Ala Lys Val Ser
 565 570 575

Glu Asp Val Ala Ile Gly Thr Lys Val Gly Asn Val Thr Ala Lys Asp
 580 585 590

Pro Glu Gly Leu Asp Ile Ser Tyr Ser Leu Arg Gly Asp Thr Arg Gly
 595 600 605

Trp Leu Lys Ile Asp His Val Thr Gly Glu Ile Phe Ser Val Ala Pro
 610 615 620

Leu Asp Arg Glu Ala Gly Ser Pro Tyr Arg Val Gln Val Val Ala Thr
 625 630 635 640

Glu Val Gly Gly Ser Ser Leu Ser Ser Val Ser Glu Phe His Leu Ile
 645 650 655

Leu Met Asp Val Asn Asp Asn Pro Pro Arg Leu Ala Lys Asp Tyr Thr
 660 665 670

Gly Leu Phe Phe Cys His Pro Leu Ser Ala Pro Gly Ser Leu Ile Phe
 675 680 685

Glu Ala Thr Asp Asp Asp Gln His Leu Phe Arg Gly Pro His Phe Thr
 690 695 700

Phe Ser Leu Gly Ser Gly Ser Leu Gln Asn Asp Trp Glu Val Ser Lys
 705 710 715 720

Ile Asn Gly Thr His Ala Arg Leu Ser Thr Arg His Thr Glu Phe Glu
 725 730 735

Glu Arg Glu Tyr Val Val Leu Ile Arg Ile Asn Asp Gly Gly Arg Pro

740

745

750

Pro Leu Glu Gly Ile Val Ser Leu Pro Val Thr Phe Cys Ser Cys Val
 755 760 765

Glu Gly Ser Cys Phe Arg Pro Ala Gly His Gln Thr Gly Ile Pro Thr
 770 775 780

Val Gly Met Ala Val Gly Ile Leu Leu Thr Thr Leu Leu Val Ile Gly
 785 790 795 800

Ile Ile Leu Ala Val Val Phe Ile Arg Ile Lys Lys Asp Lys Gly Lys
 805 810 815

Asp Asn Val Glu Ser Ala Gln Ala Ser Glu Val Lys Pro Leu Arg Ser
 820 825 830

<210> 68
 <211> 344
 <212> PRT
 <213> Homo sapiens

<400> 68

Met Gly Pro Pro Ser Ala Pro Pro Cys Arg Leu His Val Pro Trp Lys
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Glu Val Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
 20 25 30

Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
 35 40 45

Lys Glu Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly
 50 55 60

Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val
 65 70 75 80

Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
 85 90 95

Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val
 100 105 110

Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp
 115 120 125

Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu
 130 135 140
 Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys
 145 150 155 160
 Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr
 165 170 175
 Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
 180 185 190
 Leu Ser Asn Gly Asn Met Thr Leu Thr Leu Leu Ser Val Lys Arg Asn
 195 200 205
 Asp Ala Gly Ser Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn
 210 215 220
 Arg Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp Val Pro
 225 230 235 240
 Thr Ile Ser Pro Ser Lys Ala Asn Tyr Arg Pro Gly Glu Asn Leu Asn
 245 250 255
 Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe
 260 265 270
 Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
 275 280 285
 Ile Thr Val Asn Asn Ser Gly Ser Tyr Met Cys Gln Ala His Asn Ser
 290 295 300
 Ala Thr Gly Leu Asn Arg Thr Thr Val Thr Met Ile Thr Val Ser Gly
 305 310 315 320
 Ser Ala Pro Val Leu Ser Ala Val Ala Thr Val Gly Ile Thr Ile Gly
 325 330 335
 Val Leu Ala Arg Val Ala Leu Ile
 340

<210> 69
 <211> 100
 <212> PRT
 <213> Homo sapiens

<400> 69

Met Asp Ser Phe Ser Gln Asp Val Lys Thr Arg Leu Leu Ile Met Ile
 1 5 10 15

Arg Leu Leu Pro Pro Phe Asn Leu Ser Leu Leu Met Pro Ala Ser Phe
 20 25 30

Ala Trp Gln Asp Asp Ala Val Ile Ser Ile Ser Gln Glu Val Ala Ser
 35 40 45

Glu Gly Asn Leu Thr Glu Cys Gln Ile Tyr Leu Val Asn Pro Asn Val
 50 55 60

Leu His Lys Ile Arg Asp Pro Leu Val His Pro Val Thr Asp Ile Ser
 65 70 75 80

Ser Ile Phe Asn Thr Ala Val Cys Ser Asn Val Gln Trp Ser Phe Ser
 85 90 95

Glu Leu Asp Phe
 100

<210> 70

<211> 135

<212> PRT

<213> Homo sapiens

<400> 70

Met Ala Cys Gly Leu Val Ala Ser Asn Leu Asn Leu Lys Pro Gly Glu
 1 5 10 15

Cys Leu Arg Val Arg Gly Glu Val Ala Pro Asp Ala Lys Ser Phe Val
 20 25 30

Leu Asn Leu Gly Lys Asp Ser Asn Asn Leu Cys Leu His Phe Asn Pro
 35 40 45

Arg Phe Asn Ala His Gly Asp Ala Asn Thr Ile Val Cys Asn Ser Lys
 50 55 60

Asp Gly Gly Ala Trp Gly Thr Glu Gln Arg Glu Ala Val Phe Pro Phe
 65 70 75 80

Gln Pro Gly Ser Val Ala Glu Val Cys Ile Thr Phe Asp Gln Ala Asn
 85 90 95

Leu Thr Val Lys Leu Pro Asp Gly Tyr Glu Phe Lys Phe Pro Asn Arg
 100 105 110

Leu Asn Leu Glu Ala Ile Asn Tyr Met Ala Ala Asp Gly Asp Phe Lys
 115 120 125

Ile Lys Cys Val Ala Phe Asp
 130 135

<210> 71
 <211> 492
 <212> PRT
 <213> Homo sapiens

<400> 71

Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
 1 5 10 15

Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
 20 25 30

Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
 35 40 45

Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
 50 55 60

Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
 65 70 75 80

Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
 85 90 95

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
 100 105 110

Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
 115 120 125

Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
 130 135 140

Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Val
 145 150 155 160

Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp

165

170

175

Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
 180 185 190

Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
 195 200 205

Phe Met Lys Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys
 210 215 220

Leu Tyr His Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg
 225 230 235 240

Cys Ile Ala Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile
 245 250 255

Val Gly Gly Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser
 260 265 270

Leu His Val Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro
 275 280 285

Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
 290 295 300

Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
 305 310 315 320

Phe Tyr Gly Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn
 325 330 335

Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
 340 345 350

Lys Pro Leu Thr Phe Asn Asp Leu Val Lys Pro Val Cys Leu Pro Asn
 355 360 365

Pro Gly Met Met Leu Gln Pro Glu Gln Leu Cys Trp Ile Ser Gly Trp
 370 375 380

Gly Ala Thr Glu Glu Lys Gly Lys Thr Ser Glu Val Leu Asn Ala Ala
 385 390 395 400

Lys Val Leu Leu Ile Glu Thr Gln Arg Cys Asn Ser Arg Tyr Val Tyr
 405 410 415

Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly
 420 425 430

Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser
 435 440 445

Lys Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly
 450 455 460

Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe
 465 470 475 480

Thr Asp Trp Ile Tyr Arg Gln Met Arg Ala Asp Gly
 485 490

<210> 72
 <211> 2448
 <212> PRT
 <213> Homo sapiens

<400> 72

Met Ser Val Gly Arg Arg Lys Leu Ala Leu Leu Trp Ala Leu Ala Leu
 1 5 10 15

Ala Leu Ala Cys Thr Arg His Thr Gly His Ala Gln Asp Gly Ser Ser
 20 25 30

Glu Ser Ser Tyr Lys His His Pro Ala Leu Ser Pro Ile Ala Arg Gly
 35 40 45

Pro Ser Gly Val Pro Leu Arg Gly Ala Thr Val Phe Pro Ser Leu Arg
 50 55 60

Thr Ile Pro Val Val Arg Ala Ser Asn Pro Ala His Asn Gly Arg Val
 65 70 75 80

Cys Ser Thr Trp Gly Ser Phe His Tyr Lys Thr Phe Asp Gly Asp Val
 85 90 95

Phe Arg Phe Pro Gly Leu Cys Asn Tyr Val Phe Ser Glu His Cys Gly
 100 105 110

Ala Ala Tyr Glu Asp Phe Asn Ile Gln Leu Arg Arg Ser Gln Glu Ser
 115 120 125

Ala Ala Pro Thr Leu Ser Arg Val Leu Met Lys Val Asp Gly Val Val
130 135 140

Ile Gln Leu Thr Lys Gly Ser Val Leu Val Asn Gly His Pro Val Leu
145 150 155 160

Leu Pro Phe Ser Gln Ser Gly Val Leu Ile Gln Gln Ser Ser Ser Tyr
165 170 175

Thr Lys Val Glu Ala Arg Leu Gly Leu Val Leu Met Trp Asn His Asp
180 185 190

Asp Ser Leu Leu Leu Glu Leu Asp Thr Lys Tyr Ala Asn Lys Thr Cys
195 200 205

Gly Leu Cys Gly Asp Phe Asn Gly Met Pro Val Val Ser Glu Leu Leu
210 215 220

Ser His Asn Thr Lys Leu Thr Pro Met Glu Phe Gly Asn Leu Gln Lys
225 230 235 240

Met Asp Asp Pro Thr Glu Gln Cys Gln Asp Pro Val Pro Glu Pro Pro
245 250 255

Arg Asn Cys Ser Thr Gly Phe Gly Ile Cys Glu Glu Leu Leu His Gly
260 265 270

Gln Leu Phe Ser Gly Cys Val Ala Leu Val Asp Val Gly Ser Tyr Leu
275 280 285

Glu Ala Cys Arg Gln Asp Leu Cys Phe Cys Glu Asp Thr Asp Leu Leu
290 295 300

Ser Cys Val Cys His Thr Leu Ala Glu Tyr Ser Arg Gln Cys Thr His
305 310 315 320

Ala Gly Gly Leu Pro Gln Asp Trp Arg Gly Pro Asp Phe Cys Pro Gln
325 330 335

Lys Cys Pro Asn Asn Met Gln Tyr His Glu Cys Arg Ser Pro Cys Ala
340 345 350

Asp Thr Cys Ser Asn Gln Glu His Ser Arg Ala Cys Glu Asp His Cys
355 360 365

Val Ala Gly Cys Phe Cys Pro Glu Gly Thr Val Leu Asp Asp Ile Gly

370

375

380

Gln Thr Gly Cys Val Pro Val Ser Lys Cys Ala Cys Val Tyr Asn Gly
 385 390 395 400

Ala Ala Tyr Ala Pro Gly Ala Thr Tyr Ser Thr Asp Cys Thr Asn Cys
 405 410 415

Thr Cys Ser Gly Gly Arg Trp Ser Cys Gln Glu Val Pro Cys Pro Asp
 420 425 430

Thr Cys Ser Val Leu Gly Gly Ala His Phe Ser Thr Phe Asp Gly Lys
 435 440 445

Gln Tyr Thr Val His Gly Asp Cys Ser Tyr Val Leu Thr Lys Pro Cys
 450 455 460

Asp Ser Ser Ala Phe Thr Val Leu Ala Glu Leu Arg Arg Cys Gly Leu
 465 470 475 480

Thr Asp Ser Glu Thr Cys Leu Lys Ser Val Thr Leu Ser Leu Asp Gly
 485 490 495

Ala Gln Thr Val Val Val Ile Lys Ala Ser Gly Glu Val Phe Leu Asn
 500 505 510

Gln Ile Tyr Thr Gln Leu Pro Ile Ser Ala Ala Asn Val Thr Ile Phe
 515 520 525

Arg Pro Ser Thr Phe Phe Ile Ile Ala Gln Thr Ser Leu Gly Leu Gln
 530 535 540

Leu Asn Leu Gln Pro Val Pro Thr Met Gln Leu Phe Met Gln Leu Ala
 545 550 555 560

Pro Lys Leu Arg Gly Gln Thr Cys Gly Leu Cys Gly Asn Phe Asn Ser
 565 570 575

Ile Gln Ala Asp Asp Phe Arg Thr Leu Ser Gly Val Val Glu Ala Thr
 580 585 590

Ala Ala Ala Phe Phe Asn Thr Phe Lys Thr Gln Ala Ala Cys Pro Asn
 595 600 605

Ile Arg Asn Ser Phe Glu Asp Pro Cys Ser Leu Ser Val Glu Asn Glu
 610 615 620

Lys Tyr Ala Gln His Trp Cys Ser Gln Leu Thr Asp Ala Asp Gly Pro
625 630 635 640

Phe Gly Arg Cys His Ala Ala Val Lys Pro Gly Thr Tyr Tyr Ser Asn
645 650 655

Cys Val Phe Asp Thr Cys Asn Cys Glu Arg Ser Glu Asp Cys Leu Cys
660 665 670

Ala Ala Leu Ser Ser Tyr Val His Ala Cys Ala Ala Lys Gly Val Gln
675 680 685

Leu Gly Gly Trp Arg Asp Gly Val Cys Thr Lys Pro Met Thr Thr Cys
690 695 700

Pro Lys Ser Met Thr Tyr His Tyr His Val Ser Thr Cys Gln Pro Thr
705 710 715 720

Cys Arg Ser Leu Ser Glu Gly Asp Ile Thr Cys Ser Val Gly Phe Ile
725 730 735

Pro Val Asp Gly Cys Ile Cys Pro Lys Gly Thr Phe Leu Asp Asp Thr
740 745 750

Gly Lys Cys Val Gln Ala Ser Asn Cys Pro Cys Tyr His Arg Gly Ser
755 760 765

Met Ile Pro Asn Gly Glu Ser Val His Asp Ser Gly Ala Ile Cys Thr
770 775 780

Cys Thr His Gly Lys Leu Ser Cys Ile Gly Gly Gln Ala Pro Ala Pro
785 790 795 800

Val Cys Ala Ala Pro Met Val Phe Phe Asp Cys Arg Asn Ala Thr Pro
805 810 815

Gly Asp Thr Gly Ala Gly Cys Gln Lys Ser Cys His Thr Leu Asp Met
820 825 830

Thr Cys Tyr Ser Pro Gln Cys Val Pro Gly Cys Val Cys Pro Asp Gly
835 840 845

Leu Val Ala Asp Gly Glu Gly Gly Cys Ile Thr Ala Glu Asp Cys Pro
850 855 860

Cys Val His Asn Glu Ala Ser Tyr Arg Ala Gly Gln Thr Ile Arg Val
 865 870 875 880

Gly Cys Asn Thr Cys Thr Cys Asp Ser Arg Met Trp Arg Cys Thr Asp
 885 890 895

Asp Pro Cys Leu Ala Thr Cys Ala Val Tyr Gly Asp Gly His Tyr Leu
 900 905 910

Thr Phe Asp Gly Gln Ser Tyr Ser Phe Asn Gly Asp Cys Glu Tyr Thr
 915 920 925

Leu Val Gln Asn His Cys Gly Gly Lys Asp Ser Thr Gln Asp Ser Phe
 930 935 940

Arg Val Val Thr Glu Asn Val Pro Cys Gly Thr Thr Gly Thr Thr Cys
 945 950 955 960

Ser Lys Ala Ile Lys Ile Phe Leu Gly Gly Phe Glu Leu Lys Leu Ser
 965 970 975

His Gly Lys Val Glu Val Ile Gly Thr Asp Glu Ser Gln Glu Val Pro
 980 985 990

Tyr Thr Ile Gln Gln Met Gly Ile Tyr Leu Val Val Asp Thr Asp Ile
 995 1000 1005

Gly Leu Val Leu Leu Trp Asp Lys Lys Thr Ser Ile Phe Ile Asn 1010
 1015 1020

Leu Ser Pro Glu Phe Lys Gly Arg Val Cys Gly Leu Cys Gly Asn
 1025 1030 1035

Phe Asp Asp Ile Ala Val Asn Asp Phe Ala Thr Arg Ser Arg Ser
 1040 1045 1050

Val Val Gly Asp Val Leu Glu Phe Gly Asn Ser Trp Lys Leu Ser
 1055 1060 1065

Pro Ser Cys Pro Asp Ala Leu Ala Pro Lys Asp Pro Cys Thr Ala
 1070 1075 1080

Asn Pro Phe Arg Lys Ser Trp Ala Gln Lys Gln Cys Ser Ile Leu
 1085 1090 1095

His Gly	Pro Thr Phe Ala Ala	Cys His Ala His Val	Glu Pro Ala
1100	1105	1110	
Arg Tyr	Tyr Glu Ala Cys Val	Asn Asp Ala Cys Ala	Cys Asp Ser
1115	1120	1125	
Gly Gly	Asp Cys Glu Cys Phe	Cys Thr Ala Val Ala	Ala Tyr Ala
1130	1135	1140	
Gln Ala	Cys His Glu Val Gly	Leu Cys Val Cys Leu	Arg Thr Pro
1145	1150	1155	
Ser Ile	Cys Pro Leu Phe Cys	Asp Tyr Tyr Asn Pro	Glu Gly Gln
1160	1165	1170	
Cys Glu	Trp His Tyr Gln Pro	Cys Gly Val Pro Cys	Leu Arg Thr
1175	1180	1185	
Cys Arg	Asn Pro Arg Gly Asp	Cys Leu Arg Asp Val	Arg Gly Leu
1190	1195	1200	
Glu Gly	Cys Tyr Pro Lys Cys	Pro Pro Glu Ala Pro	Ile Phe Asp
1205	1210	1215	
Glu Asp	Lys Met Gln Cys Val	Ala Thr Cys Pro Thr	Pro Pro Leu
1220	1225	1230	
Pro Pro	Arg Cys His Val His	Gly Lys Ser Tyr Arg	Pro Gly Ala
1235	1240	1245	
Val Val	Pro Ser Asp Lys Asn	Cys Gln Ser Cys Leu	Cys Thr Glu
1250	1255	1260	
Arg Gly	Val Glu Cys Thr Tyr	Lys Ala Glu Ala Cys	Val Cys Thr
1265	1270	1275	
Tyr Asn	Gly Gln Arg Phe His	Pro Gly Asp Val Ile	Tyr His Thr
1280	1285	1290	
Thr Asp	Gly Thr Gly Gly Cys	Ile Ser Ala Arg Cys	Gly Ala Asn
1295	1300	1305	
Gly Thr	Ile Glu Arg Arg Val	Tyr Pro Cys Ser Pro	Thr Thr Pro
1310	1315	1320	
Val Pro	Pro Thr Thr Phe Ser	Phe Ser Thr Pro Pro	Leu Val Val

1325		1330		1335
Ser Ser Thr His Thr Pro Ser Asn Gly Pro Ser Ser Ala His Thr				
1340		1345		1350
Gly Pro Pro Ser Ser Ala Trp Pro Thr Thr Ala Gly Thr Ser Pro				
1355		1360		1365
Arg Thr Arg Leu Pro Thr Ala Ser Ala Ser Leu Pro Pro Val Cys				
1370		1375		1380
Gly Glu Lys Cys Leu Trp Ser Pro Trp Met Asp Val Ser Arg Pro				
1385		1390		1395
Gly Arg Gly Thr Asp Ser Gly Asp Phe Asp Thr Leu Glu Asn Leu				
1400		1405		1410
Arg Ala His Gly Tyr Arg Val Cys Glu Ser Pro Arg Ser Val Glu				
1415		1420		1425
Cys Arg Ala Glu Asp Ala Pro Gly Val Pro Leu Arg Ala Leu Gly				
1430		1435		1440
Gln Arg Val Gln Cys Ser Pro Asp Val Gly Leu Thr Cys Arg Asn				
1445		1450		1455
Arg Glu Gln Ala Ser Gly Leu Cys Tyr Asn Tyr Gln Ile Arg Val				
1460		1465		1470
Gln Cys Cys Thr Pro Leu Pro Cys Ser Thr Ser Ser Ser Pro Ala				
1475		1480		1485
Gln Thr Thr Pro Pro Thr Thr Ser Lys Thr Thr Glu Thr Arg Ala				
1490		1495		1500
Ser Gly Ser Ser Ala Pro Ser Ser Thr Pro Gly Thr Val Ser Leu				
1505		1510		1515
Ser Thr Ala Arg Thr Thr Pro Ala Pro Gly Thr Ala Thr Ser Val				
1520		1525		1530
Lys Lys Thr Phe Ser Thr Pro Ser Pro Pro Pro Val Pro Ala Thr				
1535		1540		1545
Ser Thr Ser Ser Met Ser Thr Thr Ala Pro Gly Thr Ser Val Val				
1550		1555		1560

Ser	Ser	Lys	Pro	Thr	Pro	Thr	Glu	Pro	Ser	Thr	Ser	Ser	Cys	Leu
1565						1570					1575			
Gln	Glu	Leu	Cys	Thr	Trp	Thr	Glu	Trp	Ile	Asp	Gly	Ser	Tyr	Pro
1580						1585					1590			
Ala	Pro	Gly	Ile	Asn	Gly	Gly	Asp	Phe	Asp	Thr	Phe	Gln	Asn	Leu
1595						1600					1605			
Arg	Asp	Glu	Gly	Tyr	Thr	Phe	Cys	Glu	Ser	Pro	Arg	Ser	Val	Gln
1610						1615					1620			
Cys	Arg	Ala	Glu	Ser	Phe	Pro	Asn	Thr	Pro	Leu	Ala	Asp	Leu	Gly
1625						1630					1635			
Gln	Asp	Val	Ile	Cys	Ser	His	Thr	Glu	Gly	Leu	Ile	Cys	Leu	Asn
1640						1645					1650			
Lys	Asn	Gln	Leu	Pro	Pro	Ile	Cys	Tyr	Asn	Tyr	Glu	Ile	Arg	Ile
1655						1660					1665			
Gln	Cys	Cys	Glu	Thr	Val	Asn	Val	Cys	Arg	Asp	Ile	Thr	Arg	Leu
1670						1675					1680			
Pro	Lys	Thr	Val	Ala	Thr	Thr	Arg	Pro	Thr	Pro	His	Pro	Thr	Gly
1685						1690					1695			
Ala	Gln	Thr	Gln	Thr	Thr	Phe	Thr	Thr	His	Met	Pro	Ser	Ala	Ser
1700						1705					1710			
Thr	Glu	Gln	Pro	Thr	Ala	Thr	Ser	Arg	Gly	Gly	Pro	Thr	Ala	Thr
1715						1720					1725			
Ser	Val	Thr	Gln	Gly	Thr	His	Thr	Thr	Leu	Val	Thr	Arg	Asn	Cys
1730						1735					1740			
His	Pro	Arg	Cys	Thr	Trp	Thr	Lys	Trp	Phe	Asp	Val	Asp	Phe	Pro
1745						1750					1755			
Ser	Pro	Gly	Pro	His	Gly	Gly	Asp	Lys	Glu	Thr	Tyr	Asn	Asn	Ile
1760						1765					1770			
Ile	Arg	Ser	Gly	Glu	Lys	Ile	Cys	Arg	Arg	Pro	Glu	Glu	Ile	Thr
1775						1780					1785			

Arg Val	Gln Cys Arg Ala Lys	Ser His Pro Glu Val	Ser Ile Glu
1790	1795	1800	
His Leu	Gly Gln Val Val Gln	Cys Ser Arg Glu Glu	Gly Leu Val
1805	1810	1815	
Cys Arg	Asn Gln Asp Gln Gln	Gly Pro Phe Lys Met	Cys Leu Asn
1820	1825	1830	
Tyr Glu	Val Arg Val Leu Cys	Cys Glu Thr Pro Arg	Gly Cys His
1835	1840	1845	
Met Thr	Ser Thr Pro Gly Ser	Thr Ser Ser Ser Pro	Ala Gln Thr
1850	1855	1860	
Thr Pro	Ser Thr Thr Ser Lys	Thr Thr Glu Ile Gln	Ala Ser Gly
1865	1870	1875	
Ser Ser	Ala Pro Ser Ser Thr	Pro Gly Thr Val Ser	Leu Ser Thr
1880	1885	1890	
Ala Arg	Thr Thr Pro Ala Pro	Gly Thr Ala Thr Ser	Val Lys Lys
1895	1900	1905	
Thr Phe	Ser Thr Pro Ser Pro	Pro Pro Val Pro Ala	Thr Ser Thr
1910	1915	1920	
Ser Ser	Met Ser Thr Thr Ala	Pro Gly Thr Ser Val	Val Ser Ser
1925	1930	1935	
Lys Pro	Thr Pro Thr Glu Pro	Ser Thr Ser Ser Cys	Leu Gln Glu
1940	1945	1950	
Leu Cys	Thr Trp Thr Glu Trp	Ile Asp Gly Ser Tyr	Pro Ala Pro
1955	1960	1965	
Gly Ile	Asn Gly Gly Asp Phe	Asp Thr Phe Gln Asn	Leu Arg Asp
1970	1975	1980	
Glu Gly	Tyr Thr Phe Cys Glu	Ser Pro Arg Ser Val	Gln Cys Arg
1985	1990	1995	
Ala Glu	Ser Phe Pro Asn Thr	Pro Leu Gly Arg Leu	Gly Gln Asp
2000	2005	2010	

Val	Ile	Cys	Ser	His	Thr	Glu	Gly	Leu	Ile	Cys	Leu	Asn	Lys	Asn
2015						2020					2025			
Gln	Leu	Pro	Pro	Ile	Cys	Tyr	Asn	Tyr	Glu	Ile	Arg	Ile	Gln	Cys
2030						2035					2040			
Cys	Glu	Thr	Val	Asn	Val	Cys	Arg	Asp	Ile	Thr	Arg	Pro	Pro	Lys
2045						2050					2055			
Thr	Val	Ala	Thr	Thr	Arg	Pro	Thr	Pro	His	Pro	Thr	Gly	Ala	Gln
2060						2065					2070			
Thr	Gln	Thr	Thr	Phe	Thr	Thr	His	Met	Pro	Ser	Ala	Ser	Thr	Glu
2075						2080					2085			
Gln	Pro	Thr	Ala	Thr	Ser	Arg	Gly	Gly	Pro	Thr	Ala	Thr	Ser	Val
2090						2095					2100			
Thr	Gln	Gly	Thr	His	Thr	Thr	Pro	Val	Thr	Arg	Asn	Cys	His	Pro
2105						2110					2115			
Arg	Cys	Thr	Trp	Thr	Thr	Trp	Phe	Asp	Val	Asp	Phe	Pro	Ser	Pro
2120						2125					2130			
Gly	Pro	His	Gly	Gly	Asp	Lys	Glu	Thr	Tyr	Asn	Asn	Ile	Ile	Arg
2135						2140					2145			
Ser	Gly	Glu	Lys	Ile	Cys	Arg	Arg	Pro	Glu	Glu	Ile	Thr	Arg	Leu
2150						2155					2160			
Gln	Cys	Arg	Ala	Lys	Ser	His	Pro	Glu	Val	Ser	Ile	Glu	His	Leu
2165						2170					2175			
Gly	Gln	Val	Val	Gln	Cys	Ser	Arg	Glu	Glu	Gly	Leu	Val	Cys	Arg
2180						2185					2190			
Asn	Gln	Asp	Gln	Gln	Gly	Pro	Phe	Lys	Met	Cys	Leu	Asn	Ile	Glu
2195						2200					2205			
Val	Arg	Val	Leu	Cys	Cys	Glu	Thr	Pro	Lys	Gly	Cys	Pro	Val	Thr
2210						2215					2220			
Ser	Thr	Pro	Val	Thr	Ala	Pro	Ser	Thr	Pro	Ser	Gly	Arg	Ala	Ile
2225						2230					2235			
Ser	Pro	Thr	Gln	Ser	Thr	Ser	Ser	Trp	Gln	Lys	Ser	Arg	Thr	Thr

2240		2245		2250
Thr Leu Val Thr Thr Ser Thr Thr Ser Thr Pro Gln Thr Ser Thr				
2255		2260		2265
Thr Tyr Ala His Thr Thr Ser Thr Thr Ser Ala Pro Thr Ala Arg				
2270		2275		2280
Thr Thr Ser Ala Pro Thr Thr Ser Thr Thr Ser Val Pro Thr Thr				
2285		2290		2295
Ser Thr Ile Ser Gly Pro Lys Thr Thr Pro Ser Pro Val Pro Thr				
2300		2305		2310
Thr Ser Thr Thr Ser Ala Ala Thr Thr Ser Thr Ile Ser Ala Pro				
2315		2320		2325
Thr Thr Ser Thr Thr Ser Val Pro Gly Thr Thr Pro Ser Pro Val				
2330		2335		2340
Leu Thr Thr Ser Thr Thr Ser Ala Pro Thr Thr Arg Thr Thr Ser				
2345		2350		2355
Ala Ser Pro Ala Gly Thr Thr Ser Gly Pro Gly Asn Thr Pro Ser				
2360		2365		2370
Pro Val Pro Thr Thr Ser Thr Ile Ser Ala Pro Thr Thr Ser Ile				
2375		2380		2385
Thr Ser Ala Pro Thr Thr Ser Thr Thr Ser Ala Pro Thr Ser Ser				
2390		2395		2400
Thr Thr Ser Gly Pro Gly Thr Thr Pro Ser Pro Val Pro Thr Thr				
2405		2410		2415
Ser Ile Thr Ser Ala Pro Thr Thr Ser Thr Thr Ser Ala Pro Thr				
2420		2425		2430
Thr Ser Thr Thr Ser Ala Pro Thr Thr Ser Thr Thr Ser Ala Pro				
2435		2440		2445

<210> 73
 <211> 508
 <212> PRT
 <213> Homo sapiens

<400> 73

Met Gln Arg Leu Leu Thr Pro Val Lys Arg Ile Leu Gln Leu Thr Arg
 1 5 10 15

Ala Val Gln Glu Thr Ser Leu Thr Pro Ala Arg Leu Leu Pro Val Ala
 20 25 30

His Gln Arg Phe Ser Thr Ala Ser Ala Val Pro Leu Ala Lys Thr Asp
 35 40 45

Thr Trp Pro Lys Asp Val Gly Ile Leu Ala Leu Glu Val Tyr Phe Pro
 50 55 60

Ala Gln Tyr Val Asp Gln Thr Asp Leu Glu Lys Tyr Asn Asn Val Glu
 65 70 75 80

Ala Gly Lys Tyr Thr Val Gly Leu Gly Gln Thr Arg Met Gly Phe Cys
 85 90 95

Ser Val Gln Glu Asp Ile Asn Ser Leu Cys Leu Thr Val Val Gln Arg
 100 105 110

Leu Met Glu Arg Ile Gln Leu Pro Trp Asp Ser Val Gly Arg Leu Glu
 115 120 125

Val Gly Thr Glu Thr Ile Ile Asp Lys Ser Lys Ala Val Lys Thr Val
 130 135 140

Leu Met Glu Leu Phe Gln Asp Ser Gly Asn Thr Asp Ile Glu Gly Ile
 145 150 155 160

Asp Thr Thr Asn Ala Cys Tyr Gly Gly Thr Ala Ser Leu Phe Asn Ala
 165 170 175

Ala Asn Trp Met Glu Ser Ser Ser Trp Asp Gly Arg Tyr Ala Met Val
 180 185 190

Val Cys Gly Asp Ile Ala Val Tyr Pro Ser Gly Asn Ala Arg Pro Thr
 195 200 205

Gly Gly Ala Gly Ala Val Ala Met Leu Ile Gly Pro Lys Ala Pro Leu
 210 215 220

Ala Leu Glu Arg Gly Leu Arg Gly Thr His Met Glu Asn Val Tyr Asp
 225 230 235 240

Phe Tyr Lys Pro Asn Leu Ala Ser Glu Tyr Pro Ile Val Asp Gly Lys
 245 250 255

Leu Ser Ile Gln Cys Tyr Leu Arg Ala Leu Asp Arg Cys Tyr Thr Ser
 260 265 270

Tyr Arg Lys Lys Ile Gln Asn Gln Trp Lys Gln Ala Gly Ser Asp Arg
 275 280 285

Pro Phe Thr Leu Asp Asp Leu Gln Tyr Met Ile Phe His Thr Pro Phe
 290 295 300

Cys Lys Met Val Gln Lys Ser Leu Ala Arg Leu Met Phe Asn Asp Phe
 305 310 315 320

Leu Ser Ala Ser Ser Asp Thr Gln Thr Ser Leu Tyr Lys Gly Leu Glu
 325 330 335

Ala Phe Gly Gly Leu Lys Leu Glu Asp Thr Tyr Thr Asn Lys Asp Leu
 340 345 350

Asp Lys Ala Leu Leu Lys Ala Ser Gln Asp Met Phe Asp Lys Lys Thr
 355 360 365

Lys Ala Ser Leu Tyr Leu Ser Thr His Asn Gly Asn Met Tyr Thr Ser
 370 375 380

Ser Leu Tyr Gly Cys Leu Ala Ser Leu Leu Ser His His Ser Ala Gln
 385 390 395 400

Glu Leu Ala Gly Ser Arg Ile Gly Ala Phe Ser Tyr Gly Ser Gly Leu
 405 410 415

Ala Ala Ser Phe Phe Ser Phe Arg Val Ser Gln Asp Ala Ala Pro Gly
 420 425 430

Ser Pro Leu Asp Lys Leu Val Ser Ser Thr Ser Asp Leu Pro Lys Arg
 435 440 445

Leu Ala Ser Arg Lys Cys Val Ser Pro Glu Glu Phe Thr Glu Ile Met
 450 455 460

Asn Gln Arg Glu Gln Phe Tyr His Lys Val Asn Phe Ser Pro Pro Gly
 465 470 475 480

Asp Thr Asn Ser Leu Phe Pro Gly Thr Trp Tyr Leu Glu Arg Val Asp

485

490

495

Glu Gln His Arg Arg Lys Tyr Ala Arg Arg Pro Val
 500 505

<210> 74
 <211> 165
 <212> PRT
 <213> Homo sapiens

<400> 74

Met Gly Trp Asp Leu Thr Val Lys Met Leu Ala Gly Asn Glu Phe Gln
 1 5 10 15

Val Ser Leu Ser Ser Ser Met Ser Val Ser Glu Leu Lys Ala Gln Ile
 20 25 30

Thr Gln Lys Ile Gly Val His Ala Phe Gln Gln Arg Leu Ala Val His
 35 40 45

Pro Ser Gly Val Ala Leu Gln Asp Arg Val Pro Leu Ala Ser Gln Gly
 50 55 60

Leu Gly Pro Gly Ser Thr Val Leu Leu Val Val Asp Lys Cys Asp Glu
 65 70 75 80

Pro Leu Ser Ile Leu Val Arg Asn Asn Lys Gly Arg Ser Ser Thr Tyr
 85 90 95

Glu Val Arg Leu Thr Gln Thr Val Ala His Leu Lys Gln Gln Val Ser
 100 105 110

Gly Leu Glu Gly Val Gln Asp Asp Leu Phe Trp Leu Thr Phe Glu Gly
 115 120 125

Lys Pro Leu Glu Asp Gln Leu Pro Leu Gly Glu Tyr Gly Leu Lys Pro
 130 135 140

Leu Ser Thr Val Phe Met Asn Leu Arg Leu Arg Gly Gly Gly Thr Glu
 145 150 155 160

Pro Gly Gly Arg Ser
 165

<210> 75
 <211> 480
 <212> PRT

<213> Homo sapiens

<400> 75

Met Asn Ala Ser Glu Phe Arg Arg Arg Gly Lys Glu Met Val Asp Tyr
 1 5 10 15

Val Ala Asn Tyr Met Glu Gly Ile Glu Gly Arg Gln Val Tyr Pro Asp
 20 25 30

Val Glu Pro Gly Tyr Leu Arg Pro Leu Ile Pro Ala Ala Ala Pro Gln
 35 40 45

Glu Pro Asp Thr Phe Glu Asp Ile Ile Asn Asp Val Glu Lys Ile Ile
 50 55 60

Met Pro Gly Val Thr His Trp His Ser Pro Tyr Phe Phe Ala Tyr Phe
 65 70 75 80

Pro Thr Ala Ser Ser Tyr Pro Ala Met Leu Ala Asp Met Leu Cys Gly
 85 90 95

Ala Ile Gly Cys Ile Gly Phe Ser Trp Ala Ala Ser Pro Ala Cys Thr
 100 105 110

Glu Leu Glu Thr Val Met Met Asp Trp Leu Gly Lys Met Leu Glu Leu
 115 120 125

Pro Lys Ala Phe Leu Asn Glu Lys Ala Gly Glu Gly Gly Gly Val Ile
 130 135 140

Gln Gly Ser Ala Ser Glu Ala Thr Leu Val Ala Leu Leu Ala Ala Arg
 145 150 155 160

Thr Lys Val Ile His Arg Leu Gln Ala Ala Ser Pro Glu Leu Thr Gln
 165 170 175

Ala Ala Ile Met Glu Lys Leu Val Ala Tyr Ser Ser Asp Gln Ala His
 180 185 190

Ser Ser Val Glu Arg Ala Gly Leu Ile Gly Gly Val Lys Leu Lys Ala
 195 200 205

Ile Pro Ser Asp Gly Asn Phe Ala Met Arg Ala Ser Ala Leu Gln Glu
 210 215 220

Ala Leu Glu Arg Asp Lys Ala Ala Gly Leu Ile Pro Phe Phe Met Val

225	230	235	240
Ala Thr Leu Gly Thr Thr Thr Cys Cys Ser Phe Asp Asn Leu Leu Glu	245	250	255
Val Gly Pro Ile Cys Asn Lys Glu Asp Ile Trp Leu His Val Asp Ala	260	265	270
Ala Tyr Ala Gly Ser Ala Phe Ile Cys Pro Glu Phe Arg His Leu Leu	275	280	285
Asn Gly Val Glu Phe Ala Asp Ser Phe Asn Phe Asn Pro His Lys Trp	290	295	300
Leu Leu Val Asn Phe Asp Cys Ser Ala Met Trp Val Lys Lys Arg Thr	305	310	315
Asp Leu Thr Gly Ala Phe Arg Leu Asp Pro Thr Tyr Leu Lys His Ser	325	330	335
His Gln Asp Ser Gly Leu Ile Thr Asp Tyr Arg His Trp Gln Ile Pro	340	345	350
Leu Gly Arg Arg Phe Arg Ser Leu Lys Met Trp Phe Val Phe Arg Met	355	360	365
Tyr Gly Val Lys Gly Leu Gln Ala Tyr Ile Arg Lys His Val Gln Leu	370	375	380
Ser His Glu Phe Glu Ser Leu Val Arg Gln Asp Pro Arg Phe Glu Ile	385	390	395
Cys Val Glu Val Ile Leu Gly Leu Val Cys Phe Arg Leu Lys Gly Ser	405	410	415
Asn Lys Val Asn Glu Ala Leu Leu Gln Arg Ile Asn Ser Ala Lys Lys	420	425	430
Ile His Leu Val Pro Cys His Leu Arg Asp Lys Phe Val Leu Arg Phe	435	440	445
Ala Ile Cys Ser Arg Thr Val Glu Ser Ala His Val Gln Arg Ala Trp	450	455	460
Glu His Ile Lys Glu Leu Ala Ala Asp Val Leu Arg Ala Glu Arg Glu	465	470	475
			480

<210> 76
 <211> 402
 <212> PRT
 <213> Homo sapiens

<400> 76

Met Gln Met Ser Pro Ala Leu Thr Cys Leu Val Leu Gly Leu Ala Leu
 1 5 10 15

Val Phe Gly Glu Gly Ser Ala Val His His Pro Pro Ser Tyr Val Ala
 20 25 30

His Leu Ala Ser Asp Phe Gly Val Arg Val Phe Gln Gln Val Ala Gln
 35 40 45

Ala Ser Lys Asp Arg Asn Val Val Phe Ser Pro Tyr Gly Val Ala Ser
 50 55 60

Val Leu Ala Met Leu Gln Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln
 65 70 75 80

Ile Gln Ala Ala Met Gly Phe Lys Ile Asp Asp Lys Gly Met Ala Pro
 85 90 95

Ala Leu Arg His Leu Tyr Lys Glu Leu Met Gly Pro Trp Asn Lys Asp
 100 105 110

Glu Ile Ser Thr Thr Asp Ala Ile Phe Val Gln Arg Asp Leu Lys Leu
 115 120 125

Val Gln Gly Phe Met Pro His Phe Phe Arg Leu Phe Arg Ser Thr Val
 130 135 140

Lys Gln Val Asp Phe Ser Glu Val Glu Arg Ala Arg Phe Ile Ile Asn
 145 150 155 160

Asp Trp Val Lys Thr His Thr Lys Gly Met Ile Ser Asn Leu Leu Gly
 165 170 175

Lys Gly Ala Val Asp Gln Leu Thr Arg Leu Val Leu Val Asn Ala Leu
 180 185 190

Tyr Phe Asn Gly Gln Trp Lys Thr Pro Phe Pro Asp Ser Ser Thr His
 195 200 205

Arg Arg Leu Phe His Lys Ser Asp Gly Ser Thr Val Ser Val Pro Met

210

215

220

Met Ala Gln Thr Asn Lys Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp
 225 230 235 240

Gly His Tyr Tyr Asp Ile Leu Glu Leu Pro Tyr His Gly Asp Thr Leu
 245 250 255

Ser Met Phe Ile Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala
 260 265 270

Leu Thr Asn Ile Leu Ser Ala Gln Leu Ile Ser His Trp Lys Gly Asn
 275 280 285

Met Thr Arg Leu Pro Arg Leu Leu Val Leu Pro Lys Phe Ser Leu Glu
 290 295 300

Thr Glu Val Asp Leu Arg Lys Pro Leu Glu Asn Leu Gly Met Thr Asp
 305 310 315 320

Met Phe Arg Gln Phe Gln Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu
 325 330 335

Pro Leu His Val Ala Gln Ala Leu Gln Lys Val Lys Ile Glu Val Asn
 340 345 350

Glu Ser Gly Thr Val Ala Ser Ser Ser Thr Ala Val Ile Val Ser Ala
 355 360 365

Arg Met Ala Pro Glu Glu Ile Ile Met Asp Arg Pro Phe Leu Phe Val
 370 375 380

Val Arg His Asn Pro Thr Gly Thr Val Leu Phe Met Gly Gln Val Met
 385 390 395 400

Glu Pro

<210> 77

<211> 87

<212> PRT

<213> Homo sapiens

<400> 77

Met Gln Lys Val Thr Leu Gly Leu Leu Val Phe Leu Ala Gly Phe Pro
 1 5 10 15

Val Leu Asp Ala Asn Asp Leu Glu Asp Lys Asn Ser Pro Phe Tyr Tyr
 20 25 30

Asp Trp His Ser Leu Gln Val Gly Gly Leu Ile Cys Ala Gly Val Leu
 35 40 45

Cys Ala Met Gly Ile Ile Ile Val Met Ser Ala Lys Cys Lys Cys Lys
 50 55 60

Phe Gly Gln Lys Ser Gly His His Pro Gly Glu Thr Pro Pro Leu Ile
 65 70 75 80

Thr Pro Gly Ser Ala Gln Ser
 85

<210> 78
 <211> 317
 <212> PRT
 <213> Homo sapiens

<400> 78

Met Thr Ser Arg Thr Arg Val Thr Trp Pro Ser Pro Pro Arg Pro Leu
 1 5 10 15

Pro Val Pro Ala Ala Ala Ala Val Ala Phe Gly Ala Lys Gly Thr Asp
 20 25 30

Pro Ala Glu Ala Arg Ser Ser Arg Gly Ile Glu Glu Ala Gly Pro Arg
 35 40 45

Ala His Gly Arg Ala Gly Arg Glu Pro Glu Arg Arg Arg Ser Arg Gln
 50 55 60

Gln Arg Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr
 65 70 75 80

Cys Ala Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala
 85 90 95

Pro Trp Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val
 100 105 110

Arg Thr Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala
 115 120 125

Val Val Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr

130

135

140

Asn Phe Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp
 145 150 155 160

Ala Asn Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile
 165 170 175

Cys Ala Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile
 180 185 190

Ile Pro Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu
 195 200 205

Val Ala Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile
 210 215 220

Arg Gln Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val
 225 230 235 240

Asn Pro Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile
 245 250 255

Leu Thr Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg
 260 265 270

Tyr Ile Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser
 275 280 285

Asn Asp Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn
 290 295 300

Gly Ala Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala
 305 310 315

<210> 79
 <211> 117
 <212> PRT
 <213> Homo sapiens
 <400> 79

Met Arg Ala Ser Ser Phe Leu Ile Val Val Val Phe Leu Ile Ala Gly
 1 5 10 15

Thr Leu Val Leu Glu Ala Ala Val Thr Gly Val Pro Val Lys Gly Gln
 20 25 30

Asp Thr Val Lys Gly Arg Val Pro Phe Asn Gly Gln Asp Pro Val Lys
 35 40 45

Gly Gln Val Ser Val Lys Gly Gln Asp Lys Val Lys Ala Gln Glu Pro
 50 55 60

Val Lys Gly Pro Val Ser Thr Lys Pro Gly Ser Cys Pro Ile Ile Leu
 65 70 75 80

Ile Arg Cys Ala Met Leu Asn Pro Pro Asn Arg Cys Leu Lys Asp Thr
 85 90 95

Asp Cys Pro Gly Ile Lys Lys Cys Cys Glu Gly Ser Cys Gly Met Ala
 100 105 110

Cys Phe Val Pro Gln
 115

<210> 80
 <211> 364
 <212> PRT
 <213> Homo sapiens

<400> 80

Met Val Val Pro Ser Leu Lys Leu Gln Asp Leu Ile Glu Glu Ile Arg
 1 5 10 15

Gly Ala Lys Thr Gln Ala Gln Glu Arg Glu Val Ile Gln Lys Glu Cys
 20 25 30

Ala His Ile Arg Ala Ser Phe Arg Asp Gly Asp Pro Val His Arg His
 35 40 45

Arg Gln Leu Ala Lys Leu Leu Tyr Val His Met Leu Gly Tyr Pro Ala
 50 55 60

His Phe Gly Gln Met Glu Cys Leu Lys Leu Ile Ala Ser Ser Arg Phe
 65 70 75 80

Thr Asp Lys Arg Val Gly Tyr Leu Gly Ala Met Leu Leu Leu Asp Glu
 85 90 95

Arg His Asp Ala His Leu Leu Ile Thr Asn Ser Ile Lys Asn Asp Leu
 100 105 110

Ser Gln Gly Ile Gln Pro Val Gln Gly Leu Ala Leu Cys Thr Leu Ser
 115 120 125

Thr Met Gly Ser Ala Glu Met Cys Arg Asp Leu Ala Pro Glu Val Glu
 130 135 140

Lys Leu Leu Leu Gln Pro Ser Pro Tyr Val Arg Lys Lys Ala Ile Leu
 145 150 155 160

Thr Ala Val His Met Ile Arg Lys Val Pro Glu Leu Ser Ser Val Phe
 165 170 175

Leu Pro Pro Cys Ala Gln Leu Leu His Glu Arg His His Gly Ile Leu
 180 185 190

Leu Gly Thr Ile Thr Leu Ile Thr Glu Leu Cys Glu Arg Ser Pro Ala
 195 200 205

Ala Leu Arg His Phe Arg Lys Val Val Pro Gln Leu Val His Ile Leu
 210 215 220

Arg Thr Leu Val Thr Met Gly Tyr Ser Thr Glu His Ser Ile Ser Gly
 225 230 235 240

Val Ser Asp Pro Phe Leu Gln Val Gln Ile Leu Arg Leu Leu Arg Ile
 245 250 255

Leu Gly Arg Asn His Glu Glu Ser Ser Glu Thr Met Asn Asp Leu Leu
 260 265 270

Ala Gln Val Ala Thr Asn Thr Asp Thr Ser Arg Asn Ala Gly Asn Ala
 275 280 285

Val Leu Phe Glu Thr Val Leu Thr Ile Met Asp Ile Arg Ser Ala Ala
 290 295 300

Gly Leu Arg Val Leu Ala Val Asn Ile Leu Gly Arg Phe Leu Leu Asn
 305 310 315 320

Ser Asp Arg Asn Ile Arg Tyr Val Ala Leu Thr Ser Leu Leu Arg Leu
 325 330 335

Val Gln Ser Asp His Ser Ala Val Gln Arg His Arg Pro Thr Val Val
 340 345 350

Glu Cys Leu Arg Glu Thr Asp Ala Ser Leu Ser Arg
 355 360

<210> 81
 <211> 806
 <212> PRT
 <213> Homo sapiens

<400> 81

Met Gly Ala Pro Ala Cys Ala Leu Ala Leu Cys Val Ala Val Ala Ile
 1 5 10 15

Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
 20 25 30

Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
 35 40 45

Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
 50 55 60

Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
 65 70 75 80

Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
 85 90 95

Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
 100 105 110

Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
 115 120 125

Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
 130 135 140

Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
 145 150 155 160

Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
 165 170 175

Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
 180 185 190

Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
 195 200 205

Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly

210

215

220

Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Ser Ile Arg Gln Thr
 225 230 235 240

Tyr Thr Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln
 245 250 255

Ala Gly Leu Pro Ala Asn Gln Thr Ala Val Leu Gly Ser Asp Val Glu
 260 265 270

Phe His Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Leu
 275 280 285

Lys His Val Glu Val Asn Gly Ser Lys Val Gly Pro Asp Gly Thr Pro
 290 295 300

Tyr Val Thr Val Leu Lys Thr Ala Gly Ala Asn Thr Thr Asp Lys Glu
 305 310 315 320

Leu Glu Val Leu Ser Leu His Asn Val Thr Phe Glu Asp Ala Gly Glu
 325 330 335

Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Phe Ser His His Ser Ala
 340 345 350

Trp Leu Val Val Leu Pro Ala Glu Glu Glu Leu Val Glu Ala Asp Glu
 355 360 365

Ala Gly Ser Val Tyr Ala Gly Ile Leu Ser Tyr Gly Val Gly Phe Phe
 370 375 380

Leu Phe Ile Leu Val Val Ala Ala Val Thr Leu Cys Arg Leu Arg Ser
 385 390 395 400

Pro Pro Lys Lys Gly Leu Gly Ser Pro Thr Val His Lys Ile Ser Arg
 405 410 415

Phe Pro Leu Lys Arg Gln Val Ser Leu Glu Ser Asn Ala Ser Met Ser
 420 425 430

Ser Asn Thr Pro Leu Val Arg Ile Ala Arg Leu Ser Ser Gly Glu Gly
 435 440 445

Pro Thr Leu Ala Asn Val Ser Glu Leu Glu Leu Pro Ala Asp Pro Lys
 450 455 460

Trp Glu Leu Ser Arg Ala Arg Leu Thr Leu Gly Lys Pro Leu Gly Glu
 465 470 475 480

Gly Cys Phe Gly Gln Val Val Met Ala Glu Ala Ile Gly Ile Asp Lys
 485 490 495

Asp Arg Ala Ala Lys Pro Val Thr Val Ala Val Lys Met Leu Lys Asp
 500 505 510

Asp Ala Thr Asp Lys Asp Leu Ser Asp Leu Val Ser Glu Met Glu Met
 515 520 525

Met Lys Met Ile Gly Lys His Lys Asn Ile Ile Asn Leu Leu Gly Ala
 530 535 540

Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys
 545 550 555 560

Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Arg Pro Pro Gly Leu Asp
 565 570 575

Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys
 580 585 590

Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu
 595 600 605

Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu
 610 615 620

Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg
 625 630 635 640

Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu
 645 650 655

Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr
 660 665 670

His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
 675 680 685

Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
 690 695 700

Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705 710 715 720

His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
725 730 735

Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
740 745 750

Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu
755 760 765

Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly
770 775 780

Asp Asp Ser Val Phe Ala His Asp Leu Leu Pro Pro Ala Pro Pro Ser
785 790 795 800

Ser Gly Gly Ser Arg Thr
805

<210> 82
<211> 387
<212> PRT
<213> Homo sapiens

<400> 82

Met Glu Lys Lys Asp Leu Gly Pro' Lys Pro Ala Leu Ile Gly His Arg
1 5 10 15

Gly Ala Pro Met Leu Ala Pro Glu His Thr Leu Met Ser Phe Arg Lys
20 25 30

Ala Leu Glu Gln Lys Leu Tyr Gly Leu Gln Ala Asp Ile Thr Ile Ser
35 40 45

Leu Asp Gly Val Pro Phe Leu Met His Asp Thr Thr Leu Arg Arg Thr
50 55 60

Thr Asn Val Glu Glu Glu Phe Pro Glu Leu Ala Arg Arg Pro Ala Ser
65 70 75 80

Met Leu Asn Trp Thr Thr Leu Gln Arg Leu Asn Ala Gly Gln Trp Phe
85 90 95

Leu Lys Thr Asp Pro Phe Trp Thr Ala Ser Ser Leu Ser Pro Ser Asp

100	105	110
His Arg Glu Ala Gln Asn Gln Ser Ile Cys Ser Leu Ala Glu Leu Leu		
115	120	125
Glu Leu Ala Lys Gly Asn Ala Thr Leu Leu Leu Asn Leu Arg Asp Pro		
130	135	140
Pro Arg Glu His Pro Tyr Arg Ser Ser Phe Ile Asn Val Thr Leu Glu		
145	150	155
Ala Val Leu His Ser Gly Phe Pro Gln His Gln Val Met Trp Leu Pro		
165	170	175
Ser Arg Gln Arg Pro Leu Val Arg Lys Val Ala Pro Gly Phe Gln Gln		
180	185	190
Thr Ser Gly Ser Lys Glu Ala Val Ala Ser Leu Arg Arg Gly His Ile		
195	200	205
Gln Arg Leu Asn Leu Arg Tyr Thr Gln Val Ser Arg Gln Glu Leu Arg		
210	215	220
Asp Tyr Ala Ser Trp Asn Leu Ser Val Asn Leu Tyr Thr Val Asn Ala		
225	230	235
Pro Trp Leu Phe Ser Leu Leu Trp Cys Ala Gly Val Pro Ser Val Thr		
245	250	255
Ser Asp Asn Ser His Thr Leu Ser Gln Val Pro Ser Pro Leu Trp Ile		
260	265	270
Met Pro Pro Asp Glu Tyr Cys Leu Met Trp Val Thr Ala Asp Leu Val		
275	280	285
Ser Phe Thr Leu Ile Val Gly Ile Phe Val Leu Gln Lys Trp Arg Leu		
290	295	300
Gly Gly Ile Arg Ser Tyr Asn Pro Glu Gln Ile Met Leu Ser Ala Ala		
305	310	315
Val Arg Arg Thr Ser Arg Asp Val Ser Ile Met Lys Glu Lys Leu Ile		
325	330	335
Phe Ser Glu Ile Ser Asp Gly Val Glu Val Ser Asp Val Leu Ser Val		
340	345	350

Cys Ser Asp Asn Ser Tyr Asp Thr Tyr Ala Asn Ser Thr Ala Thr Pro
 355 360 365

Val Gly Pro Arg Gly Gly Gly Ser His Thr Lys Thr Leu Ile Glu Arg
 370 375 380

Ser Gly Arg
 385

<210> 83
 <211> 117
 <212> PRT
 <213> Homo sapiens

<400> 83

Met Arg Ala Ser Ser Phe Leu Ile Val Val Val Phe Leu Ile Ala Gly
 1 5 10 15

Thr Leu Val Leu Glu Ala Ala Val Thr Gly Val Pro Val Lys Gly Gln
 20 25 30

Asp Thr Val Lys Gly Arg Val Pro Phe Asn Gly Gln Asp Pro Val Lys
 35 40 45

Gly Gln Val Ser Val Lys Gly Gln Asp Lys Val Lys Ala Gln Glu Pro
 50 55 60

Val Lys Gly Pro Val Ser Thr Lys Pro Gly Ser Cys Pro Ile Ile Leu
 65 70 75 80

Ile Arg Cys Ala Met Leu Asn Pro Pro Asn Arg Cys Leu Lys Asp Thr
 85 90 95

Asp Cys Pro Gly Ile Lys Lys Cys Cys Glu Gly Ser Cys Gly Met Ala
 100 105 110

Cys Phe Val Pro Gln
 115

<210> 84
 <211> 1684
 <212> PRT
 <213> Homo sapiens

<400> 84

Met Leu Gly Thr Ile Thr Ile Thr Val Gly Gln Arg Asp Ser Glu Asp

1	5	10	15
Val Ser Lys Arg Asp Ser Asp Lys Glu Met Ala Thr Lys Ser Ala Val	20	25	30
Val His Asp Ile Thr Asp Asp Gly Gln Glu Glu Thr Pro Glu Ile Ile	35	40	45
Glu Gln Ile Pro Ser Ser Glu Ser Asn Leu Glu Glu Leu Thr Gln Pro	50	55	60
Thr Glu Ser Gln Ala Asn Asp Ile Gly Phe Lys Lys Val Phe Lys Phe	65	70	75
Val Gly Phe Lys Phe Thr Val Lys Lys Asp Lys Thr Glu Lys Pro Asp	85	90	95
Thr Val Gln Leu Leu Thr Val Lys Lys Asp Glu Gly Glu Gly Ala Ala	100	105	110
Gly Ala Gly Asp His Lys Asp Pro Ser Leu Gly Ala Gly Glu Ala Ala	115	120	125
Ser Lys Glu Ser Glu Pro Lys Gln Ser Thr Glu Lys Pro Glu Glu Thr	130	135	140
Leu Lys Arg Glu Gln Ser His Ala Glu Ile Ser Pro Pro Ala Glu Ser	145	150	155
Gly Gln Ala Val Glu Glu Cys Lys Glu Glu Gly Glu Glu Lys Gln Glu	165	170	175
Lys Glu Pro Ser Lys Ser Ala Glu Ser Pro Thr Ser Pro Val Thr Ser	180	185	190
Glu Thr Gly Ser Thr Phe Lys Lys Phe Phe Thr Gln Gly Trp Ala Gly	195	200	205
Trp Arg Lys Lys Thr Ser Phe Arg Lys Pro Lys Glu Asp Glu Val Glu	210	215	220
Ala Ser Glu Lys Lys Lys Glu Gln Glu Pro Glu Lys Val Asp Thr Glu	225	230	235
Glu Asp Gly Lys Ala Glu Val Ala Ser Glu Lys Leu Thr Ala Ser Glu	245	250	255

Gln Ala His Pro Gln Glu Pro Ala Glu Ser Ala His Glu Pro Arg Leu
 260 265 270

Ser Ala Glu Tyr Glu Lys Val Glu Leu Pro Ser Glu Glu Gln Val Ser
 275 280 285

Gly Ser Gln Gly Pro Ser Glu Glu Lys Pro Ala Pro Leu Ala Thr Glu
 290 295 300

Val Phe Asp Glu Lys Ile Glu Val His Gln Glu Glu Val Val Ala Glu
 305 310 315 320

Val His Val Ser Thr Val Glu Glu Arg Thr Glu Glu Gln Lys Thr Glu
 325 330 335

Val Glu Glu Thr Ala Gly Ser Val Pro Ala Glu Glu Leu Val Glu Met
 340 345 350

Asp Ala Glu Pro Gln Glu Ala Glu Pro Ala Lys Glu Leu Val Lys Leu
 355 360 365

Lys Glu Thr Cys Val Ser Gly Glu Asp Pro Thr Gln Gly Ala Asp Leu
 370 375 380

Ser Pro Asp Glu Lys Val Leu Ser Lys Pro Pro Glu Gly Val Val Ser
 385 390 395 400

Glu Val Glu Met Leu Ser Ser Gln Glu Arg Met Lys Val Gln Gly Ser
 405 410 415

Pro Leu Lys Lys Leu Phe Thr Ser Thr Gly Leu Lys Lys Leu Ser Gly
 420 425 430

Lys Lys Gln Lys Gly Lys Arg Gly Gly Gly Asp Glu Glu Ser Gly Glu
 435 440 445

His Thr Gln Val Pro Ala Asp Ser Pro Asp Ser Gln Glu Glu Gln Lys
 450 455 460

Gly Glu Ser Ser Ala Ser Ser Pro Glu Glu Pro Glu Glu Ile Thr Cys
 465 470 475 480

Leu Glu Lys Gly Leu Ala Glu Val Gln Gln Asp Gly Glu Ala Glu Glu
 485 490 495

Gly Ala Thr Ser Asp Gly Glu Lys Lys Arg Glu Gly Val Thr Pro Trp
 500 505 510

Ala Ser Phe Lys Lys Met Val Thr Pro Lys Lys Arg Val Arg Arg Pro
 515 520 525

Ser Glu Ser Asp Lys Glu Asp Glu Leu Asp Lys Val Lys Ser Ala Thr
 530 535 540

Leu Ser Ser Thr Glu Ser Thr Ala Ser Glu Met Gln Glu Glu Met Lys
 545 550 555 560

Gly Ser Val Glu Glu Pro Lys Pro Glu Glu Pro Lys Arg Lys Val Asp
 565 570 575

Thr Ser Val Ser Trp Glu Ala Leu Ile Cys Val Gly Ser Ser Lys Lys
 580 585 590

Arg Ala Arg Arg Gly Ser Ser Ser Asp Glu Glu Gly Gly Pro Lys Ala
 595 600 605

Met Gly Gly Asp His Gln Lys Ala Asp Glu Ala Gly Lys Asp Lys Glu
 610 615 620

Thr Gly Thr Asp Gly Ile Leu Ala Gly Ser Gln Glu His Asp Pro Gly
 625 630 635 640

Gln Gly Ser Ser Ser Pro Glu Gln Ala Gly Ser Pro Thr Glu Gly Glu
 645 650 655

Gly Val Ser Thr Trp Glu Ser Phe Lys Arg Leu Val Thr Pro Arg Lys
 660 665 670

Lys Ser Lys Ser Lys Leu Glu Glu Lys Ser Glu Asp Ser Ile Ala Gly
 675 680 685

Ser Gly Val Glu His Ser Thr Pro Asp Thr Glu Pro Gly Lys Glu Glu
 690 695 700

Ser Trp Val Ser Ile Lys Lys Phe Ile Pro Gly Arg Arg Lys Lys Arg
 705 710 715 720

Pro Asp Gly Lys Gln Glu Gln Ala Pro Val Glu Asp Ala Gly Pro Thr
 725 730 735

Gly Ala Asn Glu Asp Asp Ser Asp Val Pro Ala Val Val Pro Leu Ser
 740 745 750

Glu Tyr Asp Ala Val Glu Arg Glu Lys Met Glu Ala Gln Gln Ala Gln
 755 760 765

Lys Ser Ala Glu Gln Pro Glu Gln Lys Ala Ala Thr Glu Val Ser Lys
 770 775 780

Glu Leu Ser Glu Ser Gln Val His Met Met Ala Ala Ala Val Ala Asp
 785 790 795 800

Gly Thr Arg Ala Ala Thr Ile Ile Glu Glu Arg Ser Pro Ser Trp Ile
 805 810 815

Ser Ala Ser Val Thr Glu Pro Leu Glu Gln Val Glu Ala Glu Ala Ala
 820 825 830

Leu Leu Thr Glu Glu Val Leu Glu Arg Glu Val Ile Ala Glu Glu Glu
 835 840 845

Pro Pro Thr Val Thr Glu Pro Leu Pro Glu Asn Arg Glu Ala Arg Gly
 850 855 860

Asp Thr Val Val Ser Glu Ala Glu Leu Thr Pro Glu Ala Val Thr Ala
 865 870 875 880

Ala Glu Thr Ala Gly Pro Leu Gly Ala Glu Glu Gly Thr Glu Ala Ser
 885 890 895

Ala Ala Glu Glu Thr Thr Glu Met Val Ser Ala Val Ser Gln Leu Thr
 900 905 910

Asp Ser Pro Asp Thr Thr Glu Glu Ala Thr Pro Val Gln Glu Val Glu
 915 920 925

Gly Gly Val Pro Asp Ile Glu Glu Gln Glu Arg Arg Thr Gln Glu Val
 930 935 940

Leu Gln Ala Val Ala Glu Lys Val Lys Glu Glu Ser Gln Leu Pro Gly
 945 950 955 960

Thr Gly Gly Pro Glu Asp Val Leu Gln Pro Val Gln Arg Ala Glu Ala
 965 970 975

Glu Arg Pro Glu Glu Gln Ala Glu Ala Ser Gly Leu Lys Lys Glu Thr

980					985					990				
Asp Val	Val Leu	Lys Val	Asp Ala	Gln Glu	Ala Lys	Thr Glu	Pro Phe							
995			1000			1005								
Thr Gln	Gly Lys	Val Val	Gly Gln	Thr Thr	Pro Glu	Ser Phe	Glu							
1010			1015			1020								
Lys Ala	Pro Gln	Val Thr	Glu Ser	Ile Glu	Ser Ser	Glu Leu	Val							
1025			1030			1035								
Thr Thr	Cys Gln	Ala Glu	Thr Leu	Ala Gly	Val Lys	Ser Gln	Glu							
1040			1045			1050								
Met Val	Met Glu	Gln Ala	Ile Pro	Pro Asp	Ser Val	Glu Thr	Pro							
1055			1060			1065								
Thr Asp	Ser Glu	Thr Asp	Gly Ser	Thr Pro	Val Ala	Asp Phe	Asp							
1070			1075			1080								
Ala Pro	Gly Thr	Thr Gln	Lys Asp	Glu Ile	Val Glu	Ile His	Glu							
1085			1090			1095								
Glu Asn	Glu Val	Ala Ser	Gly Thr	Gln Ser	Gly Gly	Thr Glu	Ala							
1100			1105			1110								
Glu Ala	Val Pro	Ala Gln	Lys Glu	Arg Pro	Pro Ala	Pro Ser	Ser							
1115			1120			1125								
Phe Val	Phe Gln	Glu Glu	Thr Lys	Glu Gln	Ser Lys	Met Glu	Asp							
1130			1135			1140								
Thr Leu	Glu His	Thr Asp	Lys Glu	Val Ser	Val Glu	Thr Val	Ser							
1145			1150			1155								
Ile Leu	Ser Lys	Thr Glu	Gly Thr	Gln Glu	Ala Asp	Gln Tyr	Ala							
1160			1165			1170								
Asp Glu	Lys Thr	Lys Asp	Val Pro	Phe Phe	Glu Gly	Leu Glu	Gly							
1175			1180			1185								
Ser Ile	Asp Thr	Gly Ile	Thr Val	Ser Arg	Glu Lys	Val Thr	Glu							
1190			1195			1200								
Val Ala	Leu Lys	Gly Glu	Gly Thr	Glu Glu	Ala Glu	Cys Lys	Lys							
1205			1210			1215								

Asp	Asp	Ala	Leu	Glu	Leu	Gln	Ser	His	Ala	Lys	Ser	Pro	Pro	Ser
1220						1225					1230			
Pro	Val	Glu	Arg	Glu	Met	Val	Val	Gln	Val	Glu	Arg	Glu	Lys	Thr
1235						1240					1245			
Glu	Ala	Glu	Pro	Thr	His	Val	Asn	Glu	Glu	Lys	Leu	Glu	His	Glu
1250						1255					1260			
Thr	Ala	Val	Thr	Val	Ser	Glu	Glu	Val	Ser	Lys	Gln	Leu	Leu	Gln
1265						1270					1275			
Thr	Val	Asn	Val	Pro	Ile	Ile	Asp	Gly	Ala	Lys	Glu	Val	Ser	Ser
1280						1285					1290			
Leu	Glu	Gly	Ser	Pro	Pro	Pro	Cys	Leu	Gly	Gln	Glu	Glu	Ala	Val
1295						1300					1305			
Cys	Thr	Lys	Ile	Gln	Val	Gln	Ser	Ser	Glu	Ala	Ser	Phe	Thr	Leu
1310						1315					1320			
Thr	Ala	Ala	Ala	Glu	Glu	Glu	Lys	Val	Leu	Gly	Glu	Thr	Ala	Asn
1325						1330					1335			
Ile	Leu	Glu	Thr	Gly	Glu	Thr	Leu	Glu	Pro	Ala	Gly	Ala	His	Leu
1340						1345					1350			
Val	Leu	Glu	Glu	Lys	Ser	Ser	Glu	Lys	Asn	Glu	Asp	Phe	Ala	Ala
1355						1360					1365			
His	Pro	Gly	Glu	Asp	Ala	Val	Pro	Thr	Gly	Pro	Asp	Cys	Gln	Ala
1370						1375					1380			
Lys	Ser	Thr	Pro	Val	Ile	Val	Ser	Ala	Thr	Thr	Lys	Lys	Gly	Leu
1385						1390					1395			
Ser	Ser	Asp	Leu	Glu	Gly	Glu	Lys	Thr	Thr	Ser	Leu	Lys	Trp	Lys
1400						1405					1410			
Ser	Asp	Glu	Val	Asp	Glu	Gln	Val	Ala	Cys	Gln	Glu	Val	Lys	Val
1415						1420					1425			
Ser	Val	Ala	Ile	Glu	Asp	Leu	Glu	Pro	Glu	Asn	Gly	Ile	Leu	Glu
1430						1435					1440			

Leu Glu Thr Lys Ser Ser Lys	Leu Val Gln Asn Ile	Ile Gln Thr
1445	1450	1455
Ala Val Asp Gln Phe Val Arg	Thr Glu Glu Thr Ala	Thr Glu Met
1460	1465	1470
Leu Thr Ser Glu Leu Gln Thr	Gln Ala His Val Ile	Lys Ala Asp
1475	1480	1485
Ser Gln Asp Ala Gly Gln Glu	Thr Glu Lys Glu Gly	Glu Glu Pro
1490	1495	1500
Leu Ala Ser Ala Gln Asp Glu	Thr Pro Ile Thr Ser	Ala Lys Glu
1505	1510	1515
Glu Ser Glu Ser Thr Ala Val	Gly Gln Ala His Ser	Asp Ile Ser
1520	1525	1530
Lys Asp Met Ser Glu Ala Ser	Glu Lys Thr Met Thr	Val Glu Val
1535	1540	1545
Glu Gly Ser Thr Val Asn Asp	Gln Gln Leu Glu Glu	Val Val Leu
1550	1555	1560
Pro Ser Glu Glu Glu Gly Gly	Gly Ala Gly Thr Lys	Ser Val Pro
1565	1570	1575
Glu Asp Asp Gly His Ala Leu	Leu Ala Glu Arg Ile	Glu Lys Ser
1580	1585	1590
Leu Val Glu Pro Lys Glu Asp	Glu Lys Gly Asp Asp	Val Asp Asp
1595	1600	1605
Pro Glu Asn Gln Asn Ser Ala	Leu Ala Asp Thr Asp	Ala Ser Gly
1610	1615	1620
Gly Leu Thr Lys Glu Ser Pro	Asp Thr Asn Gly Pro	Lys Gln Lys
1625	1630	1635
Glu Lys Glu Asp Ala Gln Glu	Val Glu Leu Gln Glu	Gly Lys Val
1640	1645	1650
His Ser Glu Ser Asp Lys Ala	Ile Thr Pro Gln Ala	Gln Glu Glu
1655	1660	1665

Leu Gln Lys Gln Glu Arg Glu Ser Ala Lys Ser Glu Leu Thr Glu
 1670 1675 1680

Ser

<210> 85
 <211> 1722
 <212> PRT
 <213> Homo sapiens

<400> 85

Met Arg Thr Gly Trp Ala Thr Pro Arg Arg Pro Ala Gly Leu Leu Met
 1 5 10 15

Leu Leu Phe Trp Phe Phe Asp Leu Ala Glu Pro Ser Gly Arg Ala Ala
 20 25 30

Asn Asp Pro Phe Thr Ile Val His Gly Asn Thr Gly Lys Cys Ile Lys
 35 40 45

Pro Val Tyr Gly Trp Ile Val Ala Asp Asp Cys Asp Glu Thr Glu Asp
 50 55 60

Lys Leu Trp Lys Trp Val Ser Gln His Arg Leu Phe His Leu His Ser
 65 70 75 80

Gln Lys Cys Leu Gly Leu Asp Ile Thr Lys Ser Val Asn Glu Leu Arg
 85 90 95

Met Phe Ser Cys Asp Ser Ser Ala Met Leu Trp Trp Lys Cys Glu His
 100 105 110

His Ser Leu Tyr Gly Ala Ala Arg Tyr Arg Leu Ala Leu Lys Asp Gly
 115 120 125

His Gly Thr Ala Ile Ser Asn Ala Ser Asp Val Trp Lys Lys Gly Gly
 130 135 140

Ser Glu Glu Ser Leu Cys Asp Gln Pro Tyr His Glu Ile Tyr Thr Arg
 145 150 155 160

Asp Gly Asn Ser Tyr Gly Arg Pro Cys Glu Phe Pro Phe Leu Ile Asp
 165 170 175

Gly Thr Trp His His Asp Cys Ile Leu Asp Glu Asp His Ser Gly Pro
 180 185 190

Trp Cys Ala Thr Thr Leu Asn Tyr Glu Tyr Asp Arg Lys Trp Gly Ile
 195 200 205

Cys Leu Lys Pro Glu Asn Gly Cys Glu Asp Asn Trp Glu Lys Asn Glu
 210 215 220

Gln Phe Gly Ser Cys Tyr Gln Phe Asn Thr Gln Thr Ala Leu Ser Trp
 225 230 235 240

Lys Glu Ala Tyr Val Ser Cys Gln Asn Gln Gly Ala Asp Leu Leu Ser
 245 250 255

Ile Asn Ser Ala Ala Glu Leu Thr Tyr Leu Lys Glu Lys Glu Gly Ile
 260 265 270

Ala Lys Ile Phe Trp Ile Gly Leu Asn Gln Leu Tyr Ser Ala Arg Gly
 275 280 285

Trp Glu Trp Ser Asp His Lys Pro Leu Asn Phe Leu Asn Trp Asp Pro
 290 295 300

Asp Arg Pro Ser Ala Pro Thr Ile Gly Gly Ser Ser Cys Ala Arg Met
 305 310 315 320

Asp Ala Glu Ser Gly Leu Trp Gln Ser Phe Ser Cys Glu Ala Gln Leu
 325 330 335

Pro Tyr Val Cys Arg Lys Pro Leu Asn Asn Thr Val Glu Leu Thr Asp
 340 345 350

Val Trp Thr Tyr Ser Asp Thr Arg Cys Asp Ala Gly Trp Leu Pro Asn
 355 360 365

Asn Gly Phe Cys Tyr Leu Leu Val Asn Glu Ser Asn Ser Trp Asp Lys
 370 375 380

Ala His Ala Lys Cys Lys Ala Phe Ser Ser Asp Leu Ile Ser Ile His
 385 390 395 400

Ser Leu Ala Asp Val Glu Val Val Val Thr Lys Leu His Asn Glu Asp
 405 410 415

Ile Lys Glu Glu Val Trp Ile Gly Leu Lys Asn Ile Asn Ile Pro Thr
 420 425 430

Leu Phe Gln Trp Ser Asp Gly Thr Glu Val Thr Leu Thr Tyr Trp Asp
 435 440 445

Glu Asn Glu Pro Asn Val Pro Tyr Asn Lys Thr Pro Asn Cys Val Ser
 450 455 460

Tyr Leu Gly Glu Leu Gly Gln Trp Lys Val Gln Ser Cys Glu Glu Lys
 465 470 475 480

Leu Lys Tyr Val Cys Lys Arg Lys Gly Glu Lys Leu Asn Asp Ala Ser
 485 490 495

Ser Asp Lys Met Cys Pro Pro Asp Glu Gly Trp Lys Arg His Gly Glu
 500 505 510

Thr Cys Tyr Lys Ile Tyr Glu Asp Glu Val Pro Phe Gly Thr Asn Cys
 515 520 525

Asn Leu Thr Ile Thr Ser Arg Phe Glu Gln Glu Tyr Leu Asn Asp Leu
 530 535 540

Met Lys Lys Tyr Asp Lys Ser Leu Arg Lys Tyr Phe Trp Thr Gly Leu
 545 550 555 560

Arg Asp Val Asp Ser Cys Gly Glu Tyr Asn Trp Ala Thr Val Gly Gly
 565 570 575

Arg Arg Arg Ala Val Thr Phe Ser Asn Trp Asn Phe Leu Glu Pro Ala
 580 585 590

Ser Pro Gly Gly Cys Val Ala Met Ser Thr Gly Lys Ser Val Gly Lys
 595 600 605

Trp Glu Val Lys Asp Cys Arg Ser Phe Lys Ala Leu Ser Ile Cys Lys
 610 615 620

Lys Met Ser Gly Pro Leu Gly Pro Glu Glu Ala Ser Pro Lys Pro Asp
 625 630 635 640

Asp Pro Cys Pro Glu Gly Trp Gln Ser Phe Pro Ala Ser Leu Ser Cys
 645 650 655

Tyr Lys Val Phe His Ala Glu Arg Ile Val Arg Lys Arg Asn Trp Glu
 660 665 670

Glu Ala Glu Arg Phe Cys Gln Ala Leu Gly Ala His Leu Ser Ser Phe
 675 680 685

Ser His Val Asp Glu Ile Lys Glu Phe Leu His Phe Leu Thr Asp Gln
 690 695 700

Phe Ser Gly Gln His Trp Leu Trp Ile Gly Leu Asn Lys Arg Ser Pro
 705 710 715 720

Asp Leu Gln Gly Ser Trp Gln Trp Ser Asp Arg Thr Pro Val Ser Thr
 725 730 735

Ile Ile Met Pro Asn Glu Phe Gln Gln Asp Tyr Asp Ile Arg Asp Cys
 740 745 750

Ala Ala Val Lys Val Phe His Arg Pro Trp Arg Arg Gly Trp His Phe
 755 760 765

Tyr Asp Asp Arg Glu Phe Ile Tyr Leu Arg Pro Phe Ala Cys Asp Thr
 770 775 780

Lys Leu Glu Trp Val Cys Gln Ile Pro Lys Gly Arg Thr Pro Lys Thr
 785 790 795 800

Pro Asp Trp Tyr Asn Pro Asp Arg Ala Gly Ile His Gly Pro Pro Leu
 805 810 815

Ile Ile Glu Gly Ser Glu Tyr Trp Phe Val Ala Asp Leu His Leu Asn
 820 825 830

Tyr Glu Glu Ala Val Leu Tyr Cys Ala Ser Asn His Ser Phe Leu Ala
 835 840 845

Thr Ile Thr Ser Phe Val Gly Leu Lys Ala Ile Lys Asn Lys Ile Ala
 850 855 860

Asn Ile Ser Gly Asp Gly Gln Lys Trp Trp Ile Arg Ile Ser Glu Trp
 865 870 875 880

Pro Ile Asp Asp His Phe Thr Tyr Ser Arg Tyr Pro Trp His Arg Phe
 885 890 895

Pro Val Thr Phe Gly Glu Glu Cys Leu Tyr Met Ser Ala Lys Thr Trp
 900 905 910

Leu Ile Asp Leu Gly Lys Pro Thr Asp Cys Ser Thr Lys Leu Pro Phe

915	920	925
Ile Cys Glu Lys Tyr Asn Val Ser Ser Leu Glu Lys Tyr Ser Pro Asp 930 935 940		
Ser Ala Ala Lys Val Gln Cys Ser Glu Gln Trp Ile Pro Phe Gln Asn 945 950 955 960		
Lys Cys Phe Leu Lys Ile Lys Pro Val Ser Leu Thr Phe Ser Gln Ala 965 970 975		
Ser Asp Thr Cys His Ser Tyr Gly Gly Thr Leu Pro Ser Val Leu Ser 980 985 990		
Gln Ile Glu Gln Asp Phe Ile Thr Ser Leu Leu Pro Asp Met Glu Ala 995 1000 1005		
Thr Leu Trp Ile Gly Leu Arg Trp Thr Ala Tyr Glu Lys Ile Asn 1010 1015 1020		
Lys Trp Thr Asp Asn Arg Glu Leu Thr Tyr Ser Asn Phe His Pro 1025 1030 1035		
Leu Leu Val Ser Gly Arg Leu Arg Ile Pro Glu Asn Phe Phe Glu 1040 1045 1050		
Glu Glu Ser Arg Tyr His Cys Ala Leu Ile Leu Asn Leu Gln Lys 1055 1060 1065		
Ser Pro Phe Thr Gly Thr Trp Asn Phe Thr Ser Cys Ser Glu Arg 1070 1075 1080		
His Phe Val Ser Leu Cys Gln Lys Tyr Ser Glu Val Lys Ser Arg 1085 1090 1095		
Gln Thr Leu Gln Asn Ala Ser Glu Thr Val Lys Tyr Leu Asn Asn 1100 1105 1110		
Leu Tyr Lys Ile Ile Pro Lys Thr Leu Thr Trp His Ser Ala Lys 1115 1120 1125		
Arg Glu Cys Leu Lys Ser Asn Met Gln Leu Val Ser Ile Thr Asp 1130 1135 1140		
Pro Tyr Gln Gln Ala Phe Leu Ser Val Gln Ala Leu Leu His Asn 1145 1150 1155		

Ser Ser Leu Trp Ile Gly Leu Phe Ser Gln Asp Asp Glu Leu Asn
 1160 1165 1170
 Phe Gly Trp Ser Asp Gly Lys Arg Leu His Phe Ser Arg Trp Ala
 1175 1180 1185
 Glu Thr Asn Gly Gln Leu Glu Asp Cys Val Val Leu Asp Thr Asp
 1190 1195 1200
 Gly Phe Trp Lys Thr Val Asp Cys Asn Asp Asn Gln Pro Gly Ala
 1205 1210 1215
 Ile Cys Tyr Tyr Ser Gly Asn Glu Thr Glu Lys Glu Val Lys Pro
 1220 1225 1230
 Val Asp Ser Val Lys Cys Pro Ser Pro Val Leu Asn Thr Pro Trp
 1235 1240 1245
 Ile Pro Phe Gln Asn Cys Cys Tyr Asn Phe Ile Ile Thr Lys Asn
 1250 1255 1260
 Arg His Met Ala Thr Thr Gln Asp Glu Val His Thr Lys Cys Gln
 1265 1270 1275
 Lys Leu Asn Pro Lys Ser His Ile Leu Ser Ile Arg Asp Glu Lys
 1280 1285 1290
 Glu Asn Asn Phe Val Leu Glu Gln Leu Leu Tyr Phe Asn Tyr Met
 1295 1300 1305
 Ala Ser Trp Val Met Leu Gly Ile Thr Tyr Arg Asn Asn Ser Leu
 1310 1315 1320
 Met Trp Phe Asp Lys Thr Pro Leu Ser Tyr Thr His Trp Arg Ala
 1325 1330 1335
 Gly Arg Pro Thr Ile Lys Asn Glu Lys Phe Leu Ala Gly Leu Ser
 1340 1345 1350
 Thr Asp Gly Phe Trp Asp Ile Gln Thr Phe Lys Val Ile Glu Glu
 1355 1360 1365
 Ala Val Tyr Phe His Gln His Ser Ile Leu Ala Cys Lys Ile Glu
 1370 1375 1380

Met Val	Asp Tyr Lys Glu Glu	His Asn Thr Thr	Leu	Pro Gln Phe
1385		1390	1395	
Met Pro	Tyr Glu Asp Gly Ile	Tyr Ser Val Ile	Gln	Lys Lys Val
1400		1405	1410	
Thr Trp	Tyr Glu Ala Leu Asn	Met Cys Ser Gln Ser	Gly Gly His	
1415		1420	1425	
Leu Ala	Ser Val His Asn Gln	Asn Gly Gln Leu Phe	Leu Glu Asp	
1430		1435	1440	
Ile Val	Lys Arg Asp Gly Phe	Pro Leu Trp Val Gly	Leu Ser Ser	
1445		1450	1455	
His Asp	Gly Ser Glu Ser Ser	Phe Glu Trp Ser Asp	Gly Ser Thr	
1460		1465	1470	
Phe Asp	Tyr Ile Pro Trp Lys	Gly Gln Thr Ser Pro	Gly Asn Cys	
1475		1480	1485	
Val Leu	Leu Asp Pro Lys Gly	Thr Trp Lys His Glu	Lys Cys Asn	
1490		1495	1500	
Ser Val	Lys Asp Gly Ala Ile	Cys Tyr Lys Pro Thr	Lys Ser Lys	
1505		1510	1515	
Lys Leu	Ser Arg Leu Thr Tyr	Ser Ser Arg Cys Pro	Ala Ala Lys	
1520		1525	1530	
Glu Asn	Gly Ser Arg Trp Ile	Gln Tyr Lys Gly His	Cys Tyr Lys	
1535		1540	1545	
Ser Asp	Gln Ala Leu His Ser	Phe Ser Glu Ala Lys	Lys Leu Cys	
1550		1555	1560	
Ser Lys	His Asp His Ser Ala	Thr Ile Val Ser Ile	Lys Asp Glu	
1565		1570	1575	
Asp Glu	Asn Lys Phe Val Ser	Arg Leu Met Arg Glu	Asn Asn Asn	
1580		1585	1590	
Ile Thr	Met Arg Val Trp Leu	Gly Leu Ser Gln His	Ser Val Asp	
1595		1600	1605	

Gln Ser Trp Ser Trp Leu Asp Gly Ser Glu Val Thr Phe Val Lys
 1610 1615 1620

Trp Glu Asn Lys Ser Lys Ser Gly Val Gly Arg Cys Ser Met Leu
 1625 1630 1635

Ile Ala Ser Asn Glu Thr Trp Lys Lys Val Glu Cys Glu His Gly
 1640 1645 1650

Phe Gly Arg Val Val Cys Lys Val Pro Leu Gly Pro Asp Tyr Thr
 1655 1660 1665

Ala Ile Ala Ile Ile Val Ala Thr Leu Ser Ile Leu Val Leu Met
 1670 1675 1680

Gly Gly Leu Ile Trp Phe Leu Phe Gln Arg His Arg Leu His Leu
 1685 1690 1695

Ala Gly Phe Ser Ser Val Arg Tyr Ala Gln Gly Val Asn Glu Asp
 1700 1705 1710

Glu Ile Met Leu Pro Ser Phe His Asp
 1715 1720

<210> 86
 <211> 61
 <212> PRT
 <213> Homo sapiens

<400> 86

Met Asp Pro Asn Cys Ser Cys Ala Ala Gly Val Ser Cys Thr Cys Ala
 1 5 10 15

Ser Ser Cys Lys Cys Lys Glu Cys Lys Cys Thr Ser Cys Lys Lys Ser
 20 25 30

Cys Cys Ser Cys Cys Pro Val Gly Cys Ala Lys Cys Ala Gln Gly Cys
 35 40 45

Ile Cys Lys Gly Ala Ser Glu Lys Cys Ser Cys Cys Ala
 50 55 60

<210> 87
 <211> 300
 <212> PRT
 <213> Homo sapiens

<400> 87

Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
 1 5 10 15
 Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
 20 25 30
 Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
 35 40 45
 Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
 50 55 60
 Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
 65 70 75 80
 Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
 85 90 95
 Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
 100 105 110
 Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
 115 120 125
 His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
 130 135 140
 Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
 145 150 155 160
 Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
 165 170 175
 Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
 180 185 190
 Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
 195 200 205
 Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
 210 215 220
 Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
 225 230 235 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
 245 250 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
 260 265 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
 275 280 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
 290 295 300

<210> 88
 <211> 878
 <212> PRT
 <213> Homo sapiens

<400> 88

Thr Ile Tyr Ser Thr Val Ser Ser Ser Thr Thr Ala Ile Thr Ser Pro
 1 5 10 15

Phe Thr Thr Ala Glu Thr Gly Val Thr Ser Thr Pro Ser Ser Pro Ser
 20 25 30

Ser Leu Ser Thr Asp Ile Pro Thr Thr Ser Leu Arg Thr Leu Thr Pro
 35 40 45

Leu Ser Leu Ser Thr Ser Thr Ser Leu Thr Thr Thr Thr Asp Leu Pro
 50 55 60

Ser Ile Pro Thr Asp Ile Ser Ser Leu Pro Thr Pro Ile His Ile Ile
 65 70 75 80

Ser Ser Ser Pro Ser Ile Gln Ser Thr Glu Thr Ser Ser Leu Val Gly
 85 90 95

Thr Thr Ser Pro Thr Met Ser Thr Val Arg Ala Thr Leu Arg Ser Thr
 100 105 110

Glu Asn Thr Pro Ile Ser Ser Phe Ser Thr Ser Ile Val Val Thr Pro
 115 120 125

Glu Thr Pro Thr Thr Gln Ala Pro Pro Val Leu Met Ser Ala Thr Gly
 130 135 140

Thr Gln Thr Ser Pro Val Pro Thr Thr Val Thr Phe Gly Ser Met Asp
 145 150 155 160

Ser Ser Thr Ser Thr Leu His Thr Leu Thr Pro Ser Thr Ala Leu Ser
 165 170 175

Lys Ile Met Ser Thr Ser Gln Phe Pro Ile Pro Ser Thr His Ser Ser
 180 185 190

Thr Leu Gln Thr Thr Pro Ser Ile Pro Ser Leu Gln Thr Ser Leu Thr
 195 200 205

Ser Thr Ser Glu Phe Thr Thr Glu Ser Phe Thr Arg Gly Ser Thr Ser
 210 215 220

Thr Asn Ala Ile Leu Thr Ser Phe Ser Thr Ile Ile Trp Ser Ser Thr
 225 230 235 240

Pro Thr Ile Ile Met Ser Ser Ser Pro Ser Ser Ala Ser Ile Thr Pro
 245 250 255

Val Phe Ala Thr Thr Ile His Ser Val Pro Ser Ser Pro Tyr Ile Phe
 260 265 270

Ser Thr Glu Asn Val Gly Ser Ala Ser Ile Thr Ala Phe Pro Ser Leu
 275 280 285

Ser Ser Ser Ser Thr Thr Ser Thr Ser Pro Thr Ser Ser Ser Leu Thr
 290 295 300

Thr Ala Leu Thr Glu Ile Thr Pro Phe Ser Tyr Ile Ser Leu Pro Ser
 305 310 315 320

Thr Thr Pro Cys Pro Gly Thr Ile Thr Ile Thr Ile Val Pro Ala Ser
 325 330 335

Pro Thr Asp Pro Cys Val Glu Met Asp Pro Ser Thr Glu Ala Thr Ser
 340 345 350

Pro Pro Thr Thr Pro Leu Thr Val Phe Pro Phe Thr Thr Glu Met Val
 355 360 365

Thr Cys Pro Ser Ser Ile Ser Met Gln Thr Thr Leu Ala Thr His Met
 370 375 380

Asp Thr Ser Ser Met Thr Pro Glu Ser Glu Ser Ser Ile Ile Pro Asn
 385 390 395 400

Ala Ser Ser Ser Thr Gly Thr Gly Thr Val Pro Thr Asn Thr Val Phe
405 410 415

Thr Ser Thr Arg Leu Pro Thr Ser Glu Thr Trp Leu Ser Asn Asn Ser
420 425 430

Val Ile Pro Thr Pro Leu Pro Gly Val Ser Thr Ile Pro Leu Thr Met
435 440 445

Lys Pro Ser Ser Ser Leu Pro Thr Ile Leu Arg Thr Ser Ser Lys Ser
450 455 460

Thr His Pro Ser Pro Pro Thr Ala Arg Thr Ser Glu Thr Ser Val Ala
465 470 475 480

Thr Thr Gln Thr Pro Thr Thr Leu Thr Thr Arg Arg Thr Thr Pro Ile
485 490 495

Thr Ser Trp Met Thr Thr Gln Ser Thr Leu Thr Thr Thr Ala Gly Thr
500 505 510

Cys Asp Asn Gly Gly Thr Trp Glu Gln Gly Gln Cys Ala Cys Leu Pro
515 520 525

Gly Phe Ser Gly Asp Arg Cys Gln Leu Gln Thr Arg Cys Gln Asn Gly
530 535 540

Gly Gln Trp Asp Gly Leu Lys Cys Gln Cys Pro Ser Thr Phe Tyr Gly
545 550 555 560

Ser Ser Cys Glu Phe Ala Val Glu Gln Val Asp Leu Asp Val Val Glu
565 570 575

Thr Glu Val Gly Met Glu Val Ser Val Asp Gln Gln Phe Ser Pro Asp
580 585 590

Leu Asn Asp Asn Thr Ser Gln Ala Tyr Arg Asp Phe Asn Lys Thr Phe
595 600 605

Trp Asn Gln Met Gln Lys Ile Phe Ala Asp Met Gln Gly Phe Thr Phe
610 615 620

Lys Gly Val Glu Ile Leu Ser Leu Arg Asn Gly Ser Ile Val Val Asp
625 630 635 640

Tyr Leu Val Leu Leu Glu Met Pro Phe Ser Pro Gln Leu Glu Ser Glu
 645 650 655

Tyr Glu Gln Val Lys Thr Thr Leu Lys Glu Gly Leu Gln Asn Ala Ser
 660 665 670

Gln Asp Ala Asn Ser Cys Gln Asp Ser Gln Thr Leu Cys Phe Lys Pro
 675 680 685

Asp Ser Ile Lys Val Asn Asn Asn Ser Lys Thr Glu Leu Thr Pro Glu
 690 695 700

Ala Ile Cys Arg Arg Ala Ala Pro Thr Gly Tyr Glu Glu Phe Tyr Phe
 705 710 715 720

Pro Leu Val Glu Ala Thr Arg Leu Arg Cys Val Thr Lys Cys Thr Ser
 725 730 735

Gly Val Asp Asn Ala Ile Asp Cys His Gln Gly Gln Cys Val Leu Glu
 740 745 750

Thr Ser Gly Pro Ala Cys Arg Cys Tyr Ser Thr Asp Thr His Trp Phe
 755 760 765

Ser Gly Pro Arg Cys Glu Val Ala Val His Trp Arg Ala Leu Val Gly
 770 775 780

Gly Leu Thr Ala Gly Ala Ala Leu Leu Val Leu Leu Leu Leu Ala Leu
 785 790 795 800

Gly Val Arg Ala Val Arg Ser Gly Trp Trp Gly Gly Gln Arg Arg Gly
 805 810 815

Arg Ser Trp Asp Gln Asp Arg Lys Trp Phe Glu Thr Trp Asp Glu Glu
 820 825 830

Val Val Gly Thr Phe Ser Asn Trp Gly Phe Glu Asp Asp Gly Thr Asp
 835 840 845

Lys Asp Thr Asn Phe His Val Ala Leu Glu Asn Val Asp Thr Thr Met
 850 855 860

Lys Val His Ile Lys Arg Pro Glu Met Thr Ser Ser Ser Val
 865 870 875

<210> 89

<211> 61
 <212> PRT
 <213> Homo sapiens

<400> 89

Met Asp Pro Asn Cys Ser Cys Ser Pro Val Gly Ser Cys Ala Cys Ala
 1 5 10 15

Gly Ser Cys Lys Cys Lys Glu Cys Lys Cys Thr Ser Cys Lys Lys Ser
 20 25 30

Cys Cys Ser Cys Cys Pro Val Gly Cys Ala Lys Cys Ala Gln Gly Cys
 35 40 45

Ile Cys Lys Gly Thr Ser Asp Lys Cys Ser Cys Cys Ala
 50 55 60

<210> 90
 <211> 106
 <212> PRT
 <213> Homo sapiens

<400> 90

Met Ala His Ala Thr Leu Ser Ala Ala Pro Ser Asn Pro Arg Leu Leu
 1 5 10 15

Arg Val Ala Leu Leu Leu Leu Leu Val Gly Ser Arg Arg Ala Ala
 20 25 30

Gly Ala Ser Val Val Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr Leu
 35 40 45

Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Asn Val Arg Ser Pro
 50 55 60

Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn Gly
 65 70 75 80

Lys Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Gln Lys Ile Ile
 85 90 95

Glu Lys Ile Leu Asn Lys Gly Ser Thr Asn
 100 105

<210> 91
 <211> 683
 <212> PRT
 <213> Homo sapiens

<400> 91

Met Ala Leu Phe Val Arg Leu Leu Ala Leu Ala Leu Ala Leu Ala Leu
 1 5 10 15

Gly Pro Ala Ala Thr Leu Ala Gly Pro Ala Lys Ser Pro Tyr Gln Leu
 20 25 30

Val Leu Gln His Ser Arg Leu Arg Gly Arg Gln His Gly Pro Asn Val
 35 40 45

Cys Ala Val Gln Lys Val Ile Gly Thr Asn Arg Lys Tyr Phe Thr Asn
 50 55 60

Cys Lys Gln Trp Tyr Gln Arg Lys Ile Cys Gly Lys Ser Thr Val Ile
 65 70 75 80

Ser Tyr Glu Cys Cys Pro Gly Tyr Glu Lys Val Pro Gly Glu Lys Gly
 85 90 95

Cys Pro Ala Ala Leu Pro Leu Ser Asn Leu Tyr Glu Thr Leu Gly Val
 100 105 110

Val Gly Ser Thr Thr Thr Gln Leu Tyr Thr Asp Arg Thr Glu Lys Leu
 115 120 125

Arg Pro Glu Met Glu Gly Pro Gly Ser Phe Thr Ile Phe Ala Pro Ser
 130 135 140

Asn Glu Ala Trp Ala Ser Leu Pro Ala Glu Val Leu Asp Ser Leu Val
 145 150 155 160

Ser Asn Val Asn Ile Glu Leu Leu Asn Ala Leu Arg Tyr His Met Val
 165 170 175

Gly Arg Arg Val Leu Thr Asp Glu Leu Lys His Gly Met Thr Leu Thr
 180 185 190

Ser Met Tyr Gln Asn Ser Asn Ile Gln Ile His His Tyr Pro Asn Gly
 195 200 205

Ile Val Thr Val Asn Cys Ala Arg Leu Leu Lys Ala Asp His His Ala
 210 215 220

Thr Asn Gly Val Val His Leu Ile Asp Lys Val Ile Ser Thr Ile Thr
 225 230 235 240

Asn Asn Ile Gln Gln Ile Ile Glu Ile Glu Asp Thr Phe Glu Thr Leu
 245 250 255
 Arg Ala Ala Val Ala Ala Ser Gly Leu Asn Thr Met Leu Glu Gly Asn
 260 265 270
 Gly Gln Tyr Thr Leu Leu Ala Pro Thr Asn Glu Ala Phe Glu Lys Ile
 275 280 285
 Pro Ser Glu Thr Leu Asn Arg Ile Leu Gly Asp Pro Glu Ala Leu Arg
 290 295 300
 Asp Leu Leu Asn Asn His Ile Leu Lys Ser Ala Met Cys Ala Glu Ala
 305 310 315 320
 Ile Val Ala Gly Leu Ser Val Glu Thr Leu Glu Gly Thr Thr Leu Glu
 325 330 335
 Val Gly Cys Ser Gly Asp Met Leu Thr Ile Asn Gly Lys Ala Ile Ile
 340 345 350
 Ser Asn Lys Asp Ile Leu Ala Thr Asn Gly Val Ile His Tyr Ile Asp
 355 360 365
 Glu Leu Leu Ile Pro Asp Ser Ala Lys Thr Leu Phe Glu Leu Ala Ala
 370 375 380
 Glu Ser Asp Val Ser Thr Ala Ile Asp Leu Phe Arg Gln Ala Gly Leu
 385 390 395 400
 Gly Asn His Leu Ser Gly Ser Glu Arg Leu Thr Leu Leu Ala Pro Leu
 405 410 415
 Asn Ser Val Phe Lys Asp Gly Thr Pro Pro Ile Asp Ala His Thr Arg
 420 425 430
 Asn Leu Leu Arg Asn His Ile Ile Lys Asp Gln Leu Ala Ser Lys Tyr
 435 440 445
 Leu Tyr His Gly Gln Thr Leu Glu Thr Leu Gly Gly Lys Lys Leu Arg
 450 455 460
 Val Phe Val Tyr Arg Asn Ser Leu Cys Ile Glu Asn Ser Cys Ile Ala
 465 470 475 480

Ala His Asp Lys Arg Gly Arg Tyr Gly Thr Leu Phe Thr Met Asp Arg
 485 490 495

Val Leu Thr Pro Pro Met Gly Thr Val Met Asp Val Leu Lys Gly Asp
 500 505 510

Asn Arg Phe Ser Met Leu Val Ala Ala Ile Gln Ser Ala Gly Leu Thr
 515 520 525

Glu Thr Leu Asn Arg Glu Gly Val Tyr Thr Val Phe Ala Pro Thr Asn
 530 535 540

Glu Ala Phe Arg Ala Leu Pro Pro Arg Glu Arg Ser Arg Leu Leu Gly
 545 550 555 560

Asp Ala Lys Glu Leu Ala Asn Ile Leu Lys Tyr His Ile Gly Asp Glu
 565 570 575

Ile Leu Val Ser Gly Gly Ile Gly Ala Leu Val Arg Leu Lys Ser Leu
 580 585 590

Gln Gly Asp Lys Leu Glu Val Ser Leu Lys Asn Asn Val Val Ser Val
 595 600 605

Asn Lys Glu Pro Val Ala Glu Pro Asp Ile Met Ala Thr Asn Gly Val
 610 615 620

Val His Val Ile Thr Asn Val Leu Gln Pro Pro Ala Asn Arg Pro Gln
 625 630 635 640

Glu Arg Gly Asp Glu Leu Ala Asp Ser Ala Leu Glu Ile Phe Lys Gln
 645 650 655

Ala Ser Ala Phe Ser Arg Ala Ser Gln Arg Ser Val Arg Leu Ala Pro
 660 665 670

Val Tyr Gln Lys Leu Leu Glu Arg Met Lys His
 675 680

<210> 92
 <211> 431
 <212> PRT
 <213> Homo sapiens

<400> 92

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala

1	5	10	15	
Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser	20	25	30	
Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser	35	40	45	
Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu	55	60		50
Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro	65	70	75	80
Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly	85	90		95
Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser	100	105		110
Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr	115	120		125
Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys	130	135	140	
Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu	145	150	155	160
Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile	165	170		175
Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile	180	185		190
Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu	195	200	205	
Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu	210	215	220	
Val Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg	225	230	235	240
His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser	245	250		255

Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn
260 265 270

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe
275 280 285

Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser
290 295 300

Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu
305 310 315 320

Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr
325 330 335

Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
340 345 350

Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
355 360 365

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His
370 375 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
385 390 395 400

Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile
405 410 415

Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
420 425 430

<210> 93
<211> 324
<212> PRT
<213> Homo sapiens

<400> 93

Met Phe Cys Gly Asp Tyr Val Gln Gly Thr Ile Phe Pro Ala Pro Asn
1 5 10 15

Phe Asn Pro Ile Met Asp Ala Gln Met Leu Gly Gly Ala Leu Gln Gly
20 25 30

Phe Asp Cys Asp Lys Asp Met Leu Ile Asn Ile Leu Thr Gln Arg Cys
 35 40 45

Asn Ala Gln Arg Met Met Ile Ala Glu Ala Tyr Gln Ser Met Tyr Gly
 50 55 60

Arg Asp Leu Ile Gly Asp Met Lys Gly Ala Ala Phe Gly Ser Leu Pro
 65 70 75 80

Arg Cys Asp Gly Trp Leu Met Tyr Pro Pro Pro Leu Tyr Asp Ala His
 85 90 95

Glu Leu Trp His Ala Met Lys Gly Val Gly Thr Asp Glu Asn Cys Leu
 100 105 110

Ile Glu Ile Leu Ala Ser Arg Thr Asn Gly Glu Ile Phe Gln Met Arg
 115 120 125

Glu Ala Tyr Cys Leu Gln Tyr Ser Asn Asn Leu Gln Glu Asp Ile Tyr
 130 135 140

Ser Glu Thr Ser Gly His Phe Arg Asp Thr Leu Met Asn Leu Val Gln
 145 150 155 160

Gly Thr Arg Glu Glu Gly Tyr Thr Asp Pro Ala Met Ala Ala Gln Asp
 165 170 175

Ala Met Val Leu Trp Glu Ala Cys Gln Gln Lys Thr Gly Glu His Lys
 180 185 190

Thr Met Leu Gln Met Ile Leu Cys Asn Lys Ser Tyr Gln Gln Leu Arg
 195 200 205

Leu Val Phe Gln Glu Phe Gln Asn Ile Ser Gly Gln Asp Met Val Asp
 210 215 220

Ala Ile Asn Glu Cys Tyr Asp Gly Tyr Phe Gln Glu Leu Leu Val Ala
 225 230 235 240

Ile Val Leu Cys Val Arg Asp Lys Pro Ala Tyr Phe Ala Tyr Arg Leu
 245 250 255

Tyr Ser Ala Ile His Asp Phe Gly Phe His Asn Lys Thr Val Ile Arg
 260 265 270

Ile Leu Ile Ala Arg Ser Glu Ile Asp Leu Leu Thr Ile Arg Lys Arg

275

280

285

Tyr Lys Glu Arg Tyr Gly Lys Ser Leu Phe His Asp Ile Arg Asn Phe
 290 295 300

Ala Ser Gly His Tyr Lys Lys Ala Leu Leu Ala Ile Cys Ala Gly Asp
 305 310 315 320

Ala Glu Asp Tyr

<210> 94
 <211> 61
 <212> PRT
 <213> Homo sapiens

<400> 94

Met Asp Pro Asn Cys Ser Cys Ala Ala Gly Val Ser Cys Thr Cys Ala
 1 5 10 15

Gly Ser Cys Lys Cys Lys Glu Cys Lys Cys Thr Ser Cys Lys Lys Ser
 20 25 30

Cys Cys Ser Cys Cys Pro Val Gly Cys Ser Lys Cys Ala Gln Gly Cys
 35 40 45

Val Cys Lys Gly Ala Ser Glu Lys Cys Ser Cys Cys Asp
 50 55 60

<210> 95
 <211> 346
 <212> PRT
 <213> Homo sapiens

<400> 95

Met Ala Met Val Ser Glu Phe Leu Lys Gln Ala Trp Phe Ile Glu Asn
 1 5 10 15

Glu Glu Gln Glu Tyr Val Gln Thr Val Lys Ser Ser Lys Gly Gly Pro
 20 25 30

Gly Ser Ala Val Ser Pro Tyr Pro Thr Phe Asn Pro Ser Ser Asp Val
 35 40 45

Ala Ala Leu His Lys Ala Ile Met Val Lys Gly Val Asp Glu Ala Thr
 50 55 60

Ile Ile Asp Ile Leu Thr Lys Arg Asn Asn Ala Gln Arg Gln Gln Ile
 65 70 75 80

Lys Ala Ala Tyr Leu Gln Glu Thr Gly Lys Pro Leu Asp Glu Thr Leu
 85 90 95

Lys Lys Ala Leu Thr Gly His Leu Glu Glu Val Val Leu Ala Leu Leu
 100 105 110

Lys Thr Pro Ala Gln Phe Asp Ala Asp Glu Leu Arg Ala Ala Met Lys
 115 120 125

Gly Leu Gly Thr Asp Glu Asp Thr Leu Ile Glu Ile Leu Ala Ser Arg
 130 135 140

Thr Asn Lys Glu Ile Arg Asp Ile Asn Arg Val Tyr Arg Glu Glu Leu
 145 150 155 160

Lys Arg Asp Leu Ala Lys Asp Ile Thr Ser Asp Thr Ser Gly Asp Phe
 165 170 175

Arg Asn Ala Leu Leu Ser Leu Ala Lys Gly Asp Arg Ser Glu Asp Phe
 180 185 190

Gly Val Asn Glu Asp Leu Ala Asp Ser Asp Ala Arg Ala Leu Tyr Glu
 195 200 205

Ala Gly Glu Arg Arg Lys Gly Thr Asp Val Asn Val Phe Asn Thr Ile
 210 215 220

Leu Thr Thr Arg Ser Tyr Pro Gln Leu Arg Arg Val Phe Gln Lys Tyr
 225 230 235 240

Thr Lys Tyr Ser Lys His Asp Met Asn Lys Val Leu Asp Leu Glu Leu
 245 250 255

Lys Gly Asp Ile Glu Lys Cys Leu Thr Ala Ile Val Lys Cys Ala Thr
 260 265 270

Ser Lys Pro Ala Phe Phe Ala Glu Lys Leu His Gln Ala Met Lys Gly
 275 280 285

Val Gly Thr Arg His Lys Ala Leu Ile Arg Ile Met Val Ser Arg Ser
 290 295 300

Glu Ile Asp Met Asn Asp Ile Lys Ala Phe Tyr Gln Lys Met Tyr Gly
 305 310 315 320

1	5	10	15
Ser Thr Lys Ser Pro Ile Phe Gly Pro Glu Glu Val Asn Ser Val Glu	20	25	30
Gly Asn Ser Val Ser Ile Thr Cys Tyr Tyr Pro Pro Thr Ser Val Asn	35	40	45
Arg His Thr Arg Lys Tyr Trp Cys Arg Gln Gly Ala Arg Gly Gly Cys	50	55	60
Ile Thr Leu Ile Ser Ser Glu Gly Tyr Val Ser Ser Lys Tyr Ala Gly	65	70	75
Arg Ala Asn Leu Thr Asn Phe Pro Glu Asn Gly Thr Phe Val Val Asn	85	90	95
Ile Ala Gln Leu Ser Gln Asp Asp Ser Gly Arg Tyr Lys Cys Gly Leu	100	105	110
Gly Ile Asn Ser Arg Gly Leu Ser Phe Asp Val Ser Leu Glu Val Ser	115	120	125
Gln Gly Pro Gly Leu Leu Asn Asp Thr Lys Val Tyr Thr Val Asp Leu	130	135	140
Gly Arg Thr Val Thr Ile Asn Cys Pro Phe Lys Thr Glu Asn Ala Gln	145	150	155
Lys Arg Lys Ser Leu Tyr Lys Gln Ile Gly Leu Tyr Pro Val Leu Val	165	170	175
Ile Asp Ser Ser Gly Tyr Val Asn Pro Asn Tyr Thr Gly Arg Ile Arg	180	185	190
Leu Asp Ile Gln Gly Thr Gly Gln Leu Leu Phe Ser Val Val Ile Asn	195	200	205
Gln Leu Arg Leu Ser Asp Ala Gly Gln Tyr Leu Cys Gln Ala Gly Asp	210	215	220
Asp Ser Asn Ser Asn Lys Lys Asn Ala Asp Leu Gln Val Leu Lys Pro	225	230	235
Glu Pro Glu Leu Val Tyr Glu Asp Leu Arg Gly Ser Val Thr Phe His	245	250	255

Cys Ala Leu Gly Pro Glu Val Ala Asn Val Ala Lys Phe Leu Cys Arg
 260 265 270

Gln Ser Ser Gly Glu Asn Cys Asp Val Val Val Asn Thr Leu Gly Lys
 275 280 285

Arg Ala Pro Ala Phe Glu Gly Arg Ile Leu Leu Asn Pro Gln Asp Lys
 290 295 300

Asp Gly Ser Phe Ser Val Val Ile Thr Gly Leu Arg Lys Glu Asp Ala
 305 310 315 320

Gly Arg Tyr Leu Cys Gly Ala His Ser Asp Gly Gln Leu Gln Glu Gly
 325 330 335

Ser Pro Ile Gln Ala Trp Gln Leu Phe Val Asn Glu Glu Ser Thr Ile
 340 345 350

Pro Arg Ser Pro Thr Val Val Lys Gly Val Ala Gly Gly Ser Val Ala
 355 360 365

Val Leu Cys Pro Tyr Asn Arg Lys Glu Ser Lys Ser Ile Lys Tyr Trp
 370 375 380

Cys Leu Trp Glu Gly Ala Gln Asn Gly Arg Cys Pro Leu Leu Val Asp
 385 390 395 400

Ser Glu Gly Trp Val Lys Ala Gln Tyr Glu Gly Arg Leu Ser Leu Leu
 405 410 415

Glu Glu Pro Gly Asn Gly Thr Phe Thr Val Ile Leu Asn Gln Leu Thr
 420 425 430

Ser Arg Asp Ala Gly Phe Tyr Trp Cys Leu Thr Asn Gly Asp Thr Leu
 435 440 445

Trp Arg Thr Thr Val Glu Ile Lys Ile Ile Glu Gly Glu Pro Asn Leu
 450 455 460

Lys Val Pro Gly Asn Val Thr Ala Val Leu Gly Glu Thr Leu Lys Val
 465 470 475 480

Pro Cys His Phe Pro Cys Lys Phe Ser Ser Tyr Glu Lys Tyr Trp Cys
 485 490 495

Lys Trp Asn Asn Thr Gly Cys Gln Ala Leu Pro Ser Gln Asp Glu Gly
 500 505 510

Pro Ser Lys Ala Phe Val Asn Cys Asp Glu Asn Ser Arg Leu Val Ser
 515 520 525

Leu Thr Leu Asn Leu Val Thr Arg Ala Asp Glu Gly Trp Tyr Trp Cys
 530 535 540

Gly Val Lys Gln Gly His Phe Tyr Gly Glu Thr Ala Ala Val Tyr Val
 545 550 555 560

Ala Val Glu Glu Arg Lys Ala Ala Gly Ser Arg Asp Val Ser Leu Ala
 565 570 575

Lys Ala Asp Ala Ala Pro Asp Glu Lys Val Leu Asp Ser Gly Phe Arg
 580 585 590

Glu Ile Glu Asn Lys Ala Ile Gln Asp Pro Arg Leu Phe Ala Glu Glu
 595 600 605

Lys Ala Val Ala Asp Thr Arg Asp Gln Ala Asp Gly Ser Arg Ala Ser
 610 615 620

Val Asp Ser Gly Ser Ser Glu Glu Gln Gly Gly Ser Ser Arg Ala Leu
 625 630 635 640

Val Ser Thr Leu Val Pro Leu Gly Leu Val Leu Ala Val Gly Ala Val
 645 650 655

Ala Val Gly Val Ala Arg Ala Arg His Arg Lys Asn Val Asp Arg Val
 660 665 670

Ser Ile Arg Ser Tyr Arg Thr Asp Ile Ser Met Ser Asp Phe Glu Asn
 675 680 685

Ser Arg Glu Phe Gly Ala Asn Asp Asn Met Gly Ala Ser Ser Ile Thr
 690 695 700

Gln Glu Thr Ser Leu Gly Gly Lys Glu Glu Phe Val Ala Thr Thr Glu
 705 710 715 720

Ser Thr Thr Glu Thr Lys Glu Pro Lys Lys Ala Lys Arg Ser Ser Lys
 725 730 735

Glu Glu Ala Glu Met Ala Tyr Lys Asp Phe Leu Leu Gln Ser Ser Thr
 740 745 750

Val Ala Ala Glu Ala Gln Asp Gly Pro Gln Glu Ala
755 760

<210> 98
<211> 702
<212> PRT
<213> Homo sapiens

<400> 98

Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
1 5 10 15

Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
20 25 30

Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
35 40 45

Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
50 55 60

Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
65 70 75 80

Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
85 90 95

Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile
100 105 110

Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp
115 120 125

Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu
130 135 140

Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys
145 150 155 160

Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr
165 170 175

Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
180 185 190

Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn Val Thr Arg Asn
 195 200 205

Asp Thr Ala Ser Tyr Lys Cys Glu Thr Gln Asn Pro Val Ser Ala Arg
 210 215 220

Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro
 225 230 235 240

Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn
 245 250 255

Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe
 260 265 270

Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
 275 280 285

Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser
 290 295 300

Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala
 305 310 315 320

Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu
 325 330 335

Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr
 340 345 350

Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg
 355 360 365

Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr
 370 375 380

Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser
 385 390 395 400

Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp
 405 410 415

Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn
 420 425 430

Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser

435	440	445
Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile		
450	455	460
Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn		
465	470	475
Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val		
485	490	495
Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro		
500	505	510
Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln		
515	520	525
Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser		
530	535	540
Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn		
545	550	555
Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser		
565	570	575
Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly		
580	585	590
Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly		
595	600	605
Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln		
610	615	620
Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu		
625	630	635
Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly Thr Tyr Ala Cys Phe		
645	650	655
Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile		
660	665	670
Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr		
675	680	685

Val Gly Ile Met Ile Gly Val Leu Val Gly Val Ala Leu Ile
 690 695 700

<210> 99
 <211> 1015
 <212> PRT
 <213> Homo sapiens

<400> 99

Met Gly Pro Pro Leu Pro Leu Leu Leu Leu Leu Leu Leu Leu Pro
 1 5 10 15

Pro Arg Val Leu Pro Ala Ala Pro Ser Ser Val Pro Arg Gly Arg Gln
 20 25 30

Leu Pro Gly Arg Leu Gly Cys Leu Leu Glu Glu Gly Leu Cys Gly Ala
 35 40 45

Ser Glu Ala Cys Val Asn Asp Gly Val Phe Gly Arg Cys Gln Lys Val
 50 55 60

Pro Ala Met Asp Phe Tyr Arg Tyr Glu Val Ser Pro Val Ala Leu Gln
 65 70 75 80

Arg Leu Arg Val Ala Leu Gln Lys Leu Ser Gly Thr Gly Phe Thr Trp
 85 90 95

Gln Asp Asp Tyr Thr Gln Tyr Val Met Asp Gln Glu Leu Ala Asp Leu
 100 105 110

Pro Lys Thr Tyr Leu Arg Arg Pro Glu Ala Ser Ser Pro Ala Arg Pro
 115 120 125

Ser Lys His Ser Val Gly Ser Glu Arg Arg Tyr Ser Arg Glu Gly Gly
 130 135 140

Ala Ala Leu Ala Asn Ala Leu Arg Arg His Leu Pro Phe Leu Glu Ala
 145 150 155 160

Leu Ser Gln Ala Pro Ala Ser Asp Val Leu Ala Arg Thr His Thr Ala
 165 170 175

Gln Asp Arg Pro Pro Ala Glu Gly Asp Asp Arg Phe Ser Glu Ser Ile
 180 185 190

Leu Thr Tyr Val Ala His Thr Ser Ala Leu Thr Tyr Pro Pro Gly Pro
 195 200 205

Arg Thr Gln Leu Arg Glu Asp Leu Leu Pro Arg Thr Leu Gly Gln Leu
 210 215 220

Gln Pro Asp Glu Leu Ser Pro Lys Val Asp Ser Gly Val Asp Arg His
 225 230 235 240

His Leu Met Ala Ala Leu Ser Ala Tyr Ala Ala Gln Arg Pro Pro Ala
 245 250 255

Pro Pro Gly Glu Gly Ser Leu Glu Pro Gln Tyr Leu Leu Arg Ala Pro
 260 265 270

Ser Arg Met Pro Arg Pro Leu Leu Ala Pro Ala Ala Pro Gln Lys Trp
 275 280 285

Pro Ser Pro Leu Gly Asp Ser Glu Asp Pro Ser Ser Thr Gly Asp Gly
 290 295 300

Ala Arg Ile His Thr Leu Leu Lys Asp Leu Gln Arg Gln Pro Ala Glu
 305 310 315 320

Val Arg Gly Leu Ser Gly Leu Glu Leu Asp Gly Met Ala Glu Leu Met
 325 330 335

Ala Gly Leu Met Gln Gly Val Asp His Gly Val Ala Arg Gly Ser Pro
 340 345 350

Gly Arg Ala Ala Leu Gly Glu Ser Gly Glu Gln Ala Asp Gly Pro Lys
 355 360 365

Ala Thr Leu Arg Gly Asp Ser Phe Pro Asp Asp Gly Val Gln Asp Asp
 370 375 380

Asp Asp Arg Leu Tyr Gln Glu Val His Arg Leu Ser Ala Thr Leu Gly
 385 390 395 400

Gly Leu Leu Gln Asp His Gly Ser Arg Leu Leu Pro Gly Ala Leu Pro
 405 410 415

Phe Ala Arg Pro Leu Asp Met Glu Arg Lys Lys Ser Glu His Pro Glu
 420 425 430

Ser Ser Leu Ser Ser Glu Glu Glu Thr Ala Gly Val Glu Asn Val Lys

435	440	445
Ser Gln Thr Tyr Ser Lys Asp Leu Leu Gly Gln Gln Pro His Ser Glu 450 455 460		
Pro Gly Ala Ala Ala Phe Gly Glu Leu Gln Asn Gln Met Pro Gly Pro 465 470 475 480		
Ser Lys Glu Glu Gln Ser Leu Pro Ala Gly Ala Gln Glu Ala Leu Ser 485 490 495		
Asp Gly Leu Gln Leu Glu Val Gln Pro Ser Glu Glu Glu Ala Arg Gly 500 505 510		
Tyr Ile Val Thr Asp Arg Asp Pro Leu Arg Pro Glu Glu Gly Arg Arg 515 520 525		
Leu Val Glu Asp Val Ala Arg Leu Leu Gln Val Pro Ser Ser Ala Phe 530 535 540		
Ala Asp Val Glu Val Leu Gly Pro Ala Val Thr Phe Lys Val Ser Ala 545 550 555 560		
Asn Val Gln Asn Val Thr Thr Glu Asp Val Glu Lys Ala Thr Val Asp 565 570 575		
Asn Lys Asp Lys Leu Glu Glu Thr Ser Gly Leu Lys Ile Leu Gln Thr 580 585 590		
Gly Val Gly Ser Lys Ser Lys Leu Lys Phe Leu Pro Pro Gln Ala Glu 595 600 605		
Gln Glu Asp Ser Thr Lys Phe Ile Ala Leu Thr Leu Val Ser Leu Ala 610 615 620		
Cys Ile Leu Gly Val Leu Leu Ala Ser Gly Leu Ile Tyr Cys Leu Arg 625 630 635 640		
His Ser Ser Gln His Arg Leu Lys Glu Lys Leu Ser Gly Leu Gly Gly 645 650 655		
Asp Pro Gly Ala Asp Ala Thr Ala Ala Tyr Gln Glu Leu Cys Arg Gln 660 665 670		
Arg Met Ala Thr Arg Pro Pro Asp Arg Pro Glu Gly Pro His Thr Ser 675 680 685		

Arg Ile Ser Ser Val Ser Ser Gln Phe Ser Asp Gly Pro Ile Pro Ser
690 695 700

Pro Ser Ala Arg Ser Ser Ala Ser Ser Trp Ser Glu Glu Pro Val Gln
705 710 715 720

Ser Asn Met Asp Ile Ser Thr Gly His Met Ile Leu Ser Tyr Met Glu
725 730 735

Asp His Leu Lys Asn Lys Asn Arg Leu Glu Lys Glu Trp Glu Ala Leu
740 745 750

Cys Ala Tyr Gln Ala Glu Pro Asn Ser Ser Phe Val Ala Gln Arg Glu
755 760 765

Glu Asn Val Pro Lys Asn Arg Ser Leu Ala Val Leu Thr Tyr Asp His
770 775 780

Ser Arg Val Leu Leu Lys Ala Glu Asn Ser His Ser His Ser Asp Tyr
785 790 795 800

Ile Asn Ala Ser Pro Ile Met Asp His Asp Pro Arg Asn Pro Ala Tyr
805 810 815

Ile Ala Thr Gln Gly Pro Leu Pro Ala Thr Val Ala Asp Phe Trp Gln
820 825 830

Met Val Trp Glu Ser Gly Cys Val Val Ile Val Met Leu Thr Pro Leu
835 840 845

Ala Glu Asn Gly Val Arg Gln Cys Tyr His Tyr Trp Pro Asp Glu Gly
850 855 860

Ser Asn Leu Tyr His Ile Tyr Glu Val Asn Leu Val Ser Glu His Ile
865 870 875 880

Trp Cys Glu Asp Phe Leu Val Arg Ser Phe Tyr Leu Lys Asn Leu Gln
885 890 895

Thr Asn Glu Thr Arg Thr Val Thr Gln Phe His Phe Leu Ser Trp Tyr
900 905 910

Asp Arg Gly Val Pro Ser Ser Ser Arg Ser Leu Leu Asp Phe Arg Arg
915 920 925

Lys Val Asn Lys Cys Tyr Arg Gly Arg Ser Cys Pro Ile Ile Val His
 930 935 940

Cys Ser Asp Gly Ala Gly Arg Ser Gly Thr Tyr Val Leu Ile Asp Met
 945 950 955 960

Val Leu Asn Lys Met Ala Lys Gly Ala Lys Glu Ile Asp Ile Ala Ala
 965 970 975

Thr Leu Glu His Leu Arg Asp Gln Arg Pro Gly Met Val Gln Thr Lys
 980 985 990

Glu Gln Phe Glu Phe Ala Leu Thr Ala Val Ala Glu Glu Val Asn Ala
 995 1000 1005

Ile Leu Lys Ala Leu Pro Gln
 1010 1015

<210> 100
 <211> 1480
 <212> PRT
 <213> Homo sapiens

<400> 100

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1 5 10 15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
 20 25 30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
 35 40 45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
 50 55 60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
 65 70 75 80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
 85 90 95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
 100 105 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys

115	120	125
Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly 130	135	140
Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile 145	150	155 160
Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser 165	170	175
Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp 180	185	190
Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val 195	200	205
Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe 210	215	220
Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu 225	230	235 240
Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser 245	250	255
Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val 260	265	270
Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu 275	280	285
Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr 290	295	300
Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu 305	310	315 320
Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile 325	330	335
Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg 340	345	350
Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile 355	360	365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
 370 375 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
 385 390 395 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
 405 410 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
 420 425 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
 435 440 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
 450 455 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
 465 470 475 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
 485 490 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
 500 505 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
 515 520 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
 530 535 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
 545 550 555 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
 565 570 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
 580 585 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
 595 600 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu Asn Glu Gly Ser Ser
 610 615 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
 625 630 635 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
 645 650 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
 660 665 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
 675 680 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
 690 695 700

Ile Asn Ser Ile Arg Lys Phe Ser Ile Val Gln Lys Thr Pro Leu Gln
 705 710 715 720

Met Asn Gly Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu
 725 730 735

Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile Leu Pro Arg Ile
 740 745 750

Ser Val Ile Ser Thr Gly Pro Thr Leu Gln Ala Arg Arg Arg Gln Ser
 755 760 765

Val Leu Asn Leu Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His
 770 775 780

Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala
 785 790 795 800

Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr
 805 810 815

Gly Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Cys
 820 825 830

Leu Phe Asp Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr
 835 840 845

Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile
 850 855 860

Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val
 865 870 875 880

Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr
 885 890 895

His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser
 900 905 910

Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala
 915 920 925

Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val
 930 935 940

Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro
 945 950 955 960

Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe
 965 970 975

Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe
 980 985 990

Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val
 995 1000 1005

Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile
 1010 1015 1020

Val Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln
 1025 1030 1035

Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr
 1040 1045 1050

His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe
 1055 1060 1065

Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn
 1070 1075 1080

Leu His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp

1085	1090	1095
Phe Gln Met Arg Ile Glu Met 1100	Ile Phe Val Ile 1105	Phe Phe Ile Ala 1110
Val Thr Phe Ile Ser Ile Leu 1115	Thr Thr Gly Glu 1120	Gly Glu Gly Arg 1125
Val Gly Ile Ile Leu Thr 1130	Leu Ala Met Asn Ile 1135	Met Ser Thr Leu 1140
Gln Trp Ala Val Asn Ser 1145	Ser Ile Asp Val Asp 1150	Ser Leu Met Arg 1155
Ser Val Ser Arg Val Phe 1160	Lys Phe Ile Asp Met 1165	Pro Thr Glu Gly 1170
Lys Pro Thr Lys Ser Thr 1175	Lys Pro Tyr Lys Asn 1180	Gly Gln Leu Ser 1185
Lys Val Met Ile Ile Glu 1190	Asn Ser His Val Lys 1195	Lys Asp Asp Ile 1200
Trp Pro Ser Gly Gly Gln 1205	Met Thr Val Lys Asp 1210	Leu Thr Ala Lys 1215
Tyr Thr Glu Gly Gly Asn 1220	Ala Ile Leu Glu Asn 1225	Ile Ser Phe Ser 1230
Ile Ser Pro Gly Gln Arg 1235	Val Gly Leu Leu Gly 1240	Arg Thr Gly Ser 1245
Gly Lys Ser Thr Leu Leu 1250	Ser Ala Phe Leu Arg 1255	Leu Leu Asn Thr 1260
Glu Gly Glu Ile Gln Ile 1265	Asp Gly Val Ser Trp 1270	Asp Ser Ile Thr 1275
Leu Gln Gln Trp Arg Lys 1280	Ala Phe Gly Val Ile 1285	Pro Gln Lys Val 1290
Phe Ile Phe Ser Gly Thr 1295	Phe Arg Lys Asn Leu 1300	Asp Pro Tyr Glu 1305
Gln Trp Ser Asp Gln Glu 1310	Ile Trp Lys Val Ala 1315	Asp Glu Val Gly 1320

Leu Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe Val
 1325 1330 1335

Leu Val Asp Gly Gly Cys Val Leu Ser His Gly His Lys Gln Leu
 1340 1345 1350

Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu
 1355 1360 1365

Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile
 1370 1375 1380

Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val Ile
 1385 1390 1395

Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe
 1400 1405 1410

Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln
 1415 1420 1425

Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro
 1430 1435 1440

Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys
 1445 1450 1455

Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu
 1460 1465 1470

Glu Val Gln Asp Thr Arg Leu
 1475 1480

<210> 101
 <211> 270
 <212> PRT
 <213> Homo sapiens

<400> 101

Met Lys Pro Lys Met Lys Tyr Ser Thr Asn Lys Ile Ser Thr Ala Lys
 1 5 10 15

Trp Lys Asn Thr Ala Ser Lys Ala Leu Cys Phe Lys Leu Gly Lys Ser
 20 25 30

Gln Gln Lys Ala Lys Glu Val Cys Pro Met Tyr Phe Met Lys Leu Arg
 35 40 45
 Ser Gly Leu Met Ile Lys Lys Glu Ala Cys Tyr Phe Arg Arg Glu Thr
 50 55 60
 Thr Lys Arg Pro Ser Leu Lys Thr Gly Arg Lys His Lys Arg His Leu
 65 70 75 80
 Val Leu Ala Ala Cys Gln Gln Gln Ser Thr Val Glu Cys Phe Ala Phe
 85 90 95
 Gly Ile Ser Gly Val Gln Lys Tyr Thr Arg Ala Leu His Asp Ser Ser
 100 105 110
 Ile Thr Gly Ile Ser Pro Ile Thr Glu Tyr Leu Ala Ser Leu Ser Thr
 115 120 125
 Tyr Asn Asp Gln Ser Ile Thr Phe Ala Leu Glu Asp Glu Ser Tyr Glu
 130 135 140
 Ile Tyr Val Glu Asp Leu Lys Lys Asp Glu Lys Lys Asp Lys Val Leu
 145 150 155 160
 Leu Ser Tyr Tyr Glu Ser Gln His Pro Ser Asn Glu Ser Gly Asp Gly
 165 170 175
 Val Asp Gly Lys Met Leu Met Val Thr Leu Ser Pro Thr Lys Asp Phe
 180 185 190
 Trp Leu His Ala Asn Asn Lys Glu His Ser Val Glu Leu His Lys Cys
 195 200 205
 Glu Lys Pro Leu Pro Asp Gln Ala Phe Phe Val Leu His Asn Met His
 210 215 220
 Ser Asn Cys Val Ser Phe Glu Cys Lys Thr Asp Pro Gly Val Phe Ile
 225 230 235 240
 Gly Val Lys Asp Asn His Leu Ala Leu Ile Lys Val Asp Ser Ser Glu
 245 250 255
 Asn Leu Cys Thr Glu Asn Ile Leu Phe Lys Leu Ser Glu Thr
 260 265 270

<210> 102

<211> 328

<212> PRT

<213> Homo sapiens

<400> 102

Met Leu Pro Arg Val Gly Cys Pro Ala Leu Pro Leu Pro Pro Pro Pro
 1 5 10 15

Leu Leu Pro Leu Leu Pro Leu Leu Leu Leu Leu Gly Ala Ser Gly
 20 25 30

Gly Gly Gly Gly Ala Arg Ala Glu Val Leu Phe Arg Cys Pro Pro Cys
 35 40 45

Thr Pro Glu Arg Leu Ala Ala Cys Gly Pro Pro Pro Val Ala Pro Pro
 50 55 60

Ala Ala Val Ala Ala Val Ala Gly Gly Ala Arg Met Pro Cys Ala Glu
 65 70 75 80

Leu Val Arg Glu Pro Gly Cys Gly Cys Cys Ser Val Cys Ala Arg Leu
 85 90 95

Glu Gly Glu Ala Cys Gly Val Tyr Thr Pro Arg Cys Gly Gln Gly Leu
 100 105 110

Arg Cys Tyr Pro His Pro Gly Ser Glu Leu Pro Leu Gln Ala Leu Val
 115 120 125

Met Gly Glu Gly Thr Cys Glu Lys Arg Arg Asp Ala Glu Tyr Gly Ala
 130 135 140

Ser Pro Glu Gln Val Ala Asp Asn Gly Asp Asp His Ser Glu Gly Gly
 145 150 155 160

Leu Val Glu Asn His Val Asp Ser Thr Met Asn Met Leu Gly Gly Gly
 165 170 175

Gly Ser Ala Gly Arg Lys Pro Leu Lys Ser Gly Met Lys Glu Leu Ala
 180 185 190

Val Phe Arg Glu Lys Val Thr Glu Gln His Arg Gln Met Gly Lys Gly
 195 200 205

Gly Lys His His Leu Gly Leu Glu Glu Pro Lys Lys Leu Arg Pro Pro
 210 215 220

Pro Ala Arg Thr Pro Cys Gln Gln Glu Leu Asp Gln Val Leu Glu Arg
 225 230 235 240

Ile Ser Thr Met Arg Leu Pro Asp Glu Arg Gly Pro Leu Glu His Leu
 245 250 255

Tyr Ser Leu His Ile Pro Asn Cys Asp Lys His Gly Leu Tyr Asn Leu
 260 265 270

Lys Gln Cys Lys Met Ser Leu Asn Gly Gln Arg Gly Glu Cys Trp Cys
 275 280 285

Val Asn Pro Asn Thr Gly Lys Leu Ile Gln Gly Ala Pro Thr Ile Arg
 290 295 300

Gly Asp Pro Glu Cys His Leu Phe Tyr Asn Glu Gln Gln Glu Ala Cys
 305 310 315 320

Gly Val His Thr Gln Arg Met Gln
 325

<210> 103

<211> 148

<212> PRT

<213> Homo sapiens

<400> 103

Met Asp Pro Ala Pro Arg Glu Pro His Ser Thr Ser Leu Leu Leu Val
 1 5 10 15

Phe Phe Leu Phe Gly Ala Pro Leu Asp Ser Leu Pro Ser Met Lys Ala
 20 25 30

Leu Ser Pro Val Arg Gly Cys Tyr Glu Ala Val Cys Cys Leu Ser Glu
 35 40 45

Arg Ser Leu Ala Ile Ala Arg Gly Arg Gly Lys Gly Pro Ala Ala Glu
 50 55 60

Glu Pro Leu Ser Leu Leu Asp Asp Met Asn His Cys Tyr Ser Arg Leu
 65 70 75 80

Arg Glu Leu Val Pro Gly Val Pro Arg Gly Thr Gln Leu Ser Gln Val
 85 90 95

Glu Ile Leu Gln Arg Val Ile Asp Tyr Ile Leu Asp Leu Gln Val Val
 100 105 110

Leu Ala Glu Pro Ala Pro Gly Pro Pro Asp Gly Pro His Leu Pro Ile
 115 120 125

Gln Thr Ala Glu Leu Ala Pro Glu Leu Val Ile Ser Asn Asp Lys Arg
 130 135 140

Ser Phe Cys His
 145

<210> 104
 <211> 255
 <212> PRT
 <213> Homo sapiens

<400> 104

Met Ile Leu Asn Lys Ala Leu Leu Leu Gly Ala Leu Ala Leu Thr Thr
 1 5 10 15

Val Met Ser Pro Cys Gly Gly Glu Asp Ile Val Ala Asp His Val Ala
 20 25 30

Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
 35 40 45

Thr His Glu Phe Asp Gly Asp Glu Gln Phe Tyr Val Asp Leu Glu Arg
 50 55 60

Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
 65 70 75 80

Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
 85 90 95

Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
 100 105 110

Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
 115 120 125

Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
 130 135 140

Ile Thr Trp Leu Ser Asn Gly Gln Ser Val Thr Glu Asp Val Ser Glu
 145 150 155 160

Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
 165 170 175

 Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
 180 185 190

 His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
 195 200 205

 Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
 210 215 220

 Leu Ser Val Gly Leu Met Gly Ile Val Val Gly Thr Val Phe Ile Ile
 225 230 235 240

 Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
 245 250 255

<210> 105
 <211> 265
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (6)..(6)
 <223> Xaa can be any naturally occurring amino acid

<220>
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 <223> Xaa can be any naturally occurring amino acid

<220>
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 <223> Xaa can be any naturally occurring amino acid

<220>
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 <223> Xaa can be any naturally occurring amino acid

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 <222> (33)..(33)
 <223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature<222> (55)..(55)
<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

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<222> (111)..(111)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (115)..(115)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (148)..(148)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (156)..(156)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (163)..(163)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (176)..(176)
<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

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<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (256)..(256)

<223> Xaa can be any naturally occurring amino acid

<400> 105

Asn His Leu Gln Leu Xaa Arg Met Met Val Pro Xaa Ser Pro Pro Ala
1 5 10 15

Cys Arg Pro Arg Xaa Pro Xaa Cys Asn Lys Xaa Cys Cys Ser Pro Ser
20 25 30

Xaa Leu Ser Thr Arg Pro Thr Thr Tyr Thr Gly Gly Thr Pro Arg Glu
35 40 45

Pro His Leu Gly Lys Pro Xaa Gly His Gln Ser Ser Thr Cys Thr Lys
50 55 60

His Val Pro Leu Arg Gly Cys His Xaa Pro Pro Gln Thr Pro Lys Pro
65 70 75 80

Pro Pro Ala Cys Arg Ala His Gln Ser Met Ser Arg Asn Lys Trp Arg
85 90 95

Xaa Arg Xaa Ser Gln Arg Asp Ala Thr Ser Pro Pro Thr Pro Xaa Pro
100 105 110

Glu Leu Xaa Pro Ser Asp Trp Ala Cys Thr Gly Thr Asp Lys Arg His
115 120 125

Pro Glu Leu Thr Leu Gln Arg Cys Arg Gly His Pro Glu Ser Ser Phe
130 135 140

Gln Leu Ser Xaa Ser Pro Lys Val Gly Lys Leu Xaa Ile Leu Gly Ala
145 150 155 160

Tyr Gly Xaa Phe Trp Arg Arg Lys Pro Leu Ala Trp Ser Gln Lys Xaa
165 170 175

Lys Glu Leu Pro Val Pro Trp Leu Phe Cys Pro Ala Ser Pro Pro Arg
180 185 190

Glu Ala Asn Gln Trp Pro Met Trp Arg Arg Ser Pro Cys Cys Arg Ile
195 200 205

Gln Arg Leu Leu Gly Ala Xaa Leu Xaa Leu Xaa Pro Gly Asn Arg Ser
 210 215 220

Ser His Glu Thr Ser Ser Arg Leu Pro Phe Ser Gly Gln Pro Gln Arg
 225 230 235 240

Gln Pro His Asn Ala Cys His Thr Ser Tyr His Pro Ser Arg Leu Xaa
 245 250 255

Pro Ser Arg Pro Leu Ser Gly Leu Ile
 260 265

<210> 106
 <211> 907
 <212> PRT
 <213> Homo sapiens

<400> 106

Met Asp Thr Ser Arg Leu Gly Val Leu Leu Ser Leu Pro Val Leu Leu
 1 5 10 15

Gln Leu Ala Thr Gly Gly Ser Ser Pro Arg Ser Gly Val Leu Leu Arg
 20 25 30

Gly Cys Pro Thr His Cys His Cys Glu Pro Asp Gly Arg Met Leu Leu
 35 40 45

Arg Val Asp Cys Ser Asp Leu Gly Leu Ser Glu Leu Pro Ser Asn Leu
 50 55 60

Ser Val Phe Thr Ser Tyr Leu Asp Leu Ser Met Asn Asn Ile Ser Gln
 65 70 75 80

Leu Leu Pro Asn Pro Leu Pro Ser Leu Arg Phe Leu Glu Glu Leu Arg
 85 90 95

Leu Ala Gly Asn Ala Leu Thr Tyr Ile Pro Lys Gly Ala Phe Thr Gly
 100 105 110

Leu Tyr Ser Leu Lys Val Leu Met Leu Gln Asn Asn Gln Leu Arg His
 115 120 125

Val Pro Thr Glu Ala Leu Gln Asn Leu Arg Ser Leu Gln Ser Leu Arg
 130 135 140

Leu Asp Ala Asn His Ile Ser Tyr Val Pro Pro Ser Cys Phe Ser Gly
 145 150 155 160

Leu His Ser Leu Arg His Leu Trp Leu Asp Asp Asn Ala Leu Thr Glu
 165 170 175

Ile Pro Val Gln Ala Phe Arg Ser Leu Ser Ala Leu Gln Ala Met Thr
 180 185 190

Leu Ala Leu Asn Lys Ile His His Ile Pro Asp Tyr Ala Phe Gly Asn
 195 200 205

Leu Ser Ser Leu Val Val Leu His Leu His Asn Asn Arg Ile His Ser
 210 215 220

Leu Gly Lys Lys Cys Phe Asp Gly Leu His Ser Leu Glu Thr Leu Asp
 225 230 235 240

Leu Asn Tyr Asn Asn Leu Asp Glu Phe Pro Thr Ala Ile Arg Thr Leu
 245 250 255

Ser Asn Leu Lys Glu Leu Gly Phe His Ser Asn Asn Ile Arg Ser Ile
 260 265 270

Pro Glu Lys Ala Phe Val Gly Asn Pro Ser Leu Ile Thr Ile His Phe
 275 280 285

Tyr Asp Asn Pro Ile Gln Phe Val Gly Arg Ser Ala Phe Gln His Leu
 290 295 300

Pro Glu Leu Arg Thr Leu Thr Leu Asn Gly Ala Ser Gln Ile Thr Glu
 305 310 315 320

Phe Pro Asp Leu Thr Gly Thr Ala Asn Leu Glu Ser Leu Thr Leu Thr
 325 330 335

Gly Ala Gln Ile Ser Ser Leu Pro Gln Thr Val Cys Asn Gln Leu Pro
 340 345 350

Asn Leu Gln Val Leu Asp Leu Ser Tyr Asn Leu Leu Glu Asp Leu Pro
 355 360 365

Ser Phe Ser Val Cys Gln Lys Leu Gln Lys Ile Asp Leu Arg His Asn
 370 375 380

Glu Ile Tyr Glu Ile Lys Val Asp Thr Phe Gln Gln Leu Leu Ser Leu
 385 390 395 400

Arg Ser Leu Asn Leu Ala Trp Asn Lys Ile Ala Ile Ile His Pro Asn
 405 410 415

Ala Phe Ser Thr Leu Pro Ser Leu Ile Lys Leu Asp Leu Ser Ser Asn
 420 425 430

Leu Leu Ser Ser Phe Pro Ile Thr Gly Leu His Gly Leu Thr His Leu
 435 440 445

Lys Leu Thr Gly Asn His Ala Leu Gln Ser Leu Ile Ser Ser Glu Asn
 450 455 460

Phe Pro Glu Leu Lys Val Ile Glu Met Pro Tyr Ala Tyr Gln Cys Cys
 465 470 475 480

Ala Phe Gly Val Cys Glu Asn Ala Tyr Lys Ile Ser Asn Gln Trp Asn
 485 490 495

Lys Gly Asp Asn Ser Ser Met Asp Asp Leu His Lys Lys Asp Ala Gly
 500 505 510

Met Phe Gln Ala Gln Asp Glu Arg Asp Leu Glu Asp Phe Leu Leu Asp
 515 520 525

Phe Glu Glu Asp Leu Lys Ala Leu His Ser Val Gln Cys Ser Pro Ser
 530 535 540

Pro Gly Pro Phe Lys Pro Cys Glu His Leu Leu Asp Gly Trp Leu Ile
 545 550 555 560

Arg Ile Gly Val Trp Thr Ile Ala Val Leu Ala Leu Thr Cys Asn Ala
 565 570 575

Leu Val Thr Ser Thr Val Phe Arg Ser Pro Leu Tyr Ile Ser Pro Ile
 580 585 590

Lys Leu Leu Ile Gly Val Ile Ala Ala Val Asn Met Leu Thr Gly Val
 595 600 605

Ser Ser Ala Val Leu Ala Gly Val Asp Ala Phe Thr Phe Gly Ser Phe
 610 615 620

Ala Arg His Gly Ala Trp Trp Glu Asn Gly Val Gly Cys His Val Ile
 625 630 635 640

Gly Phe Leu Ser Ile Phe Ala Ser Glu Ser Ser Val Phe Leu Leu Thr
 645 650 655
 Leu Ala Ala Leu Glu Arg Gly Phe Ser Val Lys Tyr Ser Ala Lys Phe
 660 665 670
 Glu Thr Lys Ala Pro Phe Ser Ser Leu Lys Val Ile Ile Leu Leu Cys
 675 680 685
 Ala Leu Leu Ala Leu Thr Met Ala Ala Val Pro Leu Leu Gly Gly Ser
 690 695 700
 Lys Tyr Gly Ala Ser Pro Leu Cys Leu Pro Leu Pro Phe Gly Glu Pro
 705 710 715 720
 Ser Thr Met Gly Tyr Met Val Ala Leu Ile Leu Leu Asn Ser Leu Cys
 725 730 735
 Phe Leu Met Met Thr Ile Ala Tyr Thr Lys Leu Tyr Cys Asn Leu Asp
 740 745 750
 Lys Gly Asp Leu Glu Asn Ile Trp Asp Cys Ser Met Val Lys His Ile
 755 760 765
 Ala Leu Leu Leu Phe Thr Asn Cys Ile Leu Asn Cys Pro Val Ala Phe
 770 775 780
 Leu Ser Phe Ser Ser Leu Ile Asn Leu Thr Phe Ile Ser Pro Glu Val
 785 790 795 800
 Ile Lys Phe Ile Leu Leu Val Val Val Pro Leu Pro Ala Cys Leu Asn
 805 810 815
 Pro Leu Leu Tyr Ile Leu Phe Asn Pro His Phe Lys Glu Asp Leu Val
 820 825 830
 Ser Leu Arg Lys Gln Thr Tyr Val Trp Thr Arg Ser Lys His Pro Ser
 835 840 845
 Leu Met Ser Ile Asn Ser Asp Asp Val Glu Lys Gln Ser Cys Asp Ser
 850 855 860
 Thr Gln Ala Leu Val Thr Phe Thr Ser Ser Ser Ile Thr Tyr Asp Leu
 865 870 875 880
 Pro Pro Ser Ser Val Pro Ser Pro Ala Tyr Pro Val Thr Glu Ser Cys

885

890

895

His Leu Ser Ser Val Ala Phe Val Pro Cys Leu
 900 905

<210> 107
 <211> 361
 <212> PRT
 <213> Homo sapiens

<400> 107

Met Asp Pro Leu Gly Ala Ala Lys Pro Gln Trp Pro Trp Arg Arg Cys
 1 5 10 15

Leu Ala Ala Leu Leu Phe Gln Leu Leu Val Ala Val Cys Phe Phe Ser
 20 25 30

Tyr Leu Arg Val Ser Arg Asp Asp Ala Thr Gly Ser Pro Arg Ala Pro
 35 40 45

Ser Gly Ser Ser Arg Gln Asp Thr Thr Pro Thr Arg Pro Thr Leu Leu
 50 55 60

Ile Leu Leu Trp Thr Trp Pro Phe His Ile Pro Val Ala Leu Ser Arg
 65 70 75 80

Cys Ser Glu Met Val Pro Gly Thr Ala Asp Cys His Ile Thr Ala Asp
 85 90 95

Arg Lys Val Tyr Pro Gln Ala Asp Thr Val Ile Val His His Trp Asp
 100 105 110

Ile Met Ser Asn Pro Lys Ser Arg Leu Pro Pro Ser Pro Arg Pro Gln
 115 120 125

Gly Gln Arg Trp Ile Trp Phe Asn Leu Glu Pro Pro Pro Asn Cys Gln
 130 135 140

His Leu Glu Ala Leu Asp Arg Tyr Phe Asn Leu Thr Met Ser Tyr Arg
 145 150 155 160

Ser Asp Ser Asp Ile Phe Thr Pro Tyr Gly Trp Leu Glu Pro Trp Ser
 165 170 175

Gly Gln Pro Ala His Pro Pro Leu Asn Leu Ser Ala Lys Thr Glu Leu
 180 185 190

Val Ala Trp Ala Val Ser Asn Trp Lys Pro Asp Ser Ala Arg Val Arg
 195 200 205

Tyr Tyr Gln Ser Leu Gln Ala His Leu Lys Val Asp Val Tyr Gly Arg
 210 215 220

Ser His Lys Pro Leu Pro Lys Gly Thr Met Met Glu Thr Leu Ser Arg
 225 230 235 240

Tyr Lys Phe Tyr Leu Ala Phe Glu Asn Ser Leu His Pro Asp Tyr Ile
 245 250 255

Thr Glu Lys Leu Trp Arg Asn Ala Leu Glu Ala Trp Ala Val Pro Val
 260 265 270

Val Leu Gly Pro Ser Arg Ser Asn Tyr Glu Arg Phe Leu Pro Pro Asp
 275 280 285

Ala Phe Ile His Val Asp Asp Phe Gln Ser Pro Lys Asp Leu Ala Arg
 290 295 300

Tyr Leu Gln Glu Leu Asp Lys Asp His Ala Arg Tyr Leu Ser Tyr Phe
 305 310 315 320

Arg Trp Arg Glu Thr Leu Arg Pro Arg Ser Phe Ser Trp Ala Leu Asp
 325 330 335

Phe Cys Lys Ala Cys Trp Lys Leu Gln Gln Glu Ser Arg Tyr Gln Thr
 340 345 350

Val Arg Ser Ile Ala Ala Trp Phe Thr 355 360

<210> 108

<211> 122

<212> PRT

<213> Homo sapiens

<400> 108

Met Glu Ala Ser Ala Leu Thr Ser Ser Ala Val Thr Ser Val Ala Lys
 1 5 10 15

Val Val Arg Val Ala Ser Gly Ser Ala Val Val Leu Pro Leu Ala Arg
 20 25 30

Ile Ala Thr Val Val Ile Gly Gly Val Val Ala Met Ala Ala Val Pro
 35 40 45

Met Val Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser
 50 55 60

Ser Ile Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly
 65 70 75 80

Gly Val Ala Ser Gly Ser Leu Val Gly Thr Leu Gln Ser Leu Gly Ala
 85 90 95

Thr Gly Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser
 100 105 110

Ala Ile Ala Ala Val Ile Ala Arg Phe Tyr
 115 120

<210> 109
 <211> 375
 <212> PRT
 <213> Homo sapiens

<400> 109

Met Asp Ala Leu Gln Leu Ala Asn Ser Ala Phe Ala Val Asp Leu Phe
 1 5 10 15

Lys Gln Leu Cys Glu Lys Glu Pro Leu Gly Asn Val Leu Phe Ser Pro
 20 25 30

Ile Cys Leu Ser Thr Ser Leu Ser Leu Ala Gln Val Gly Ala Lys Gly
 35 40 45

Asp Thr Ala Asn Glu Ile Gly Gln Val Leu His Phe Glu Asn Val Lys
 50 55 60

Asp Ile Pro Phe Gly Phe Gln Thr Val Thr Ser Asp Val Asn Lys Leu
 65 70 75 80

Ser Ser Phe Tyr Ser Leu Lys Leu Ile Lys Arg Leu Tyr Val Asp Lys
 85 90 95

Ser Leu Asn Leu Ser Thr Glu Phe Ile Ser Ser Thr Lys Arg Pro Tyr
 100 105 110

Ala Lys Glu Leu Glu Thr Val Asp Phe Lys Asp Lys Leu Glu Glu Thr
 115 120 125

Lys Gly Gln Ile Asn Asn Ser Ile Lys Asp Leu Thr Asp Gly His Phe

130		135		140
Glu Asn Ile Leu Ala Asp Asn Ser Val Asn Asp Gln Thr Lys Ile Leu				
145		150		155 160
Val Val Asn Ala Ala Tyr Phe Val Gly Lys Trp Met Lys Lys Phe Pro				
	165		170	175
Glu Ser Glu Thr Lys Glu Cys Pro Phe Arg Leu Asn Lys Thr Asp Thr				
	180		185	190
Lys Pro Val Gln Met Met Asn Met Glu Ala Thr Phe Cys Met Gly Asn				
	195		200	205
Ile Asp Ser Ile Asn Cys Lys Ile Ile Glu Leu Pro Phe Gln Asn Lys				
210		215		220
His Leu Ser Met Phe Ile Leu Leu Pro Lys Asp Val Glu Asp Glu Ser				
225		230		235 240
Thr Gly Leu Glu Lys Ile Glu Lys Gln Leu Asn Ser Glu Ser Leu Ser				
	245		250	255
Gln Trp Thr Asn Pro Ser Thr Met Ala Asn Ala Lys Val Lys Leu Ser				
	260		265	270
Ile Pro Lys Phe Lys Val Glu Lys Met Ile Asp Pro Lys Ala Cys Leu				
	275		280	285
Glu Asn Leu Gly Leu Lys His Ile Phe Ser Glu Asp Thr Ser Asp Phe				
290		295		300
Ser Gly Met Ser Glu Thr Lys Gly Val Ala Leu Ser Asn Val Ile His				
305		310		315 320
Lys Val Cys Leu Glu Ile Thr Glu Asp Gly Gly Asp Ser Ile Glu Val				
	325		330	335
Pro Gly Ala Arg Ile Leu Gln His Lys Asp Glu Leu Asn Ala Asp His				
	340		345	350
Pro Phe Ile Tyr Ile Ile Arg His Asn Lys Thr Arg Asn Ile Ile Phe				
	355		360	365
Phe Gly Lys Phe Cys Ser Pro				
370		375		

<210> 110
 <211> 139
 <212> PRT
 <213> Homo sapiens

<400> 110

Met Asp Lys Phe Trp Trp His Ala Ala Trp Gly Leu Cys Leu Val Pro
 1 5 10 15

Leu Ser Leu Ala Gln Ile Asp Leu Asn Ile Thr Cys Arg Phe Ala Gly
 20 25 30

Val Phe His Val Glu Lys Asn Gly Arg Tyr Ser Ile Ser Arg Thr Glu
 35 40 45

Ala Ala Asp Leu Cys Lys Ala Phe Asn Ser Thr Leu Pro Thr Met Ala
 50 55 60

Gln Met Glu Lys Ala Leu Ser Ile Gly Phe Glu Thr Cys Ser Leu His
 65 70 75 80

Cys Ser Gln Gln Ser Lys Lys Val Trp Ala Glu Glu Lys Ala Ser Asp
 85 90 95

Gln Gln Trp Gln Trp Ser Cys Gly Gly Gln Lys Ala Lys Trp Thr Gln
 100 105 110

Arg Arg Gly Gln Gln Val Ser Gly Asn Gly Ala Phe Gly Glu Gln Gly
 115 120 125

Val Val Arg Asn Ser Arg Pro Val Tyr Asp Ser
 130 135

<210> 111
 <211> 535
 <212> PRT
 <213> Homo sapiens

<400> 111

Met Glu Glu Gly Ala Arg His Arg Asn Asn Thr Glu Lys Lys His Pro
 1 5 10 15

Gly Gly Gly Glu Ser Asp Ala Ser Pro Glu Ala Gly Ser Gly Gly Gly
 20 25 30

Gly Val Ala Leu Lys Lys Glu Ile Gly Leu Val Ser Ala Cys Gly Ile
 35 40 45

Ile Val Gly Asn Ile Ile Gly Ser Gly Ile Phe Val Ser Pro Lys Gly
50 55 60

Val Leu Glu Asn Ala Gly Ser Val Gly Leu Ala Leu Ile Val Trp Ile
65 70 75 80

Val Thr Gly Phe Ile Thr Val Val Gly Ala Leu Cys Tyr Ala Glu Leu
85 90 95

Gly Val Thr Ile Pro Lys Ser Gly Gly Asp Tyr Ser Tyr Val Lys Asp
100 105 110

Ile Phe Gly Gly Leu Ala Gly Phe Leu Arg Leu Trp Ile Ala Val Leu
115 120 125

Val Ile Tyr Pro Thr Asn Gln Ala Val Ile Ala Leu Thr Phe Ser Asn
130 135 140

Tyr Val Leu Gln Pro Leu Phe Pro Thr Cys Phe Pro Pro Glu Ser Gly
145 150 155 160

Leu Arg Leu Leu Ala Ala Ile Cys Leu Leu Leu Leu Thr Trp Val Asn
165 170 175

Cys Ser Ser Val Arg Trp Ala Thr Arg Val Gln Asp Ile Phe Thr Ala
180 185 190

Gly Lys Leu Leu Ala Leu Ala Leu Ile Ile Ile Met Gly Ile Val Gln
195 200 205

Ile Cys Lys Gly Glu Tyr Phe Trp Leu Glu Pro Lys Asn Ala Phe Glu
210 215 220

Asn Phe Gln Glu Pro Asp Ile Gly Leu Val Ala Leu Ala Phe Leu Gln
225 230 235 240

Gly Ser Phe Ala Tyr Gly Gly Trp Asn Phe Leu Asn Tyr Val Thr Glu
245 250 255

Glu Leu Val Asp Pro Tyr Lys Asn Leu Pro Arg Ala Ile Phe Ile Ser
260 265 270

Ile Pro Leu Val Thr Phe Val Tyr Val Phe Ala Asn Val Ala Tyr Val
275 280 285

Thr Ala Met Ser Pro Gln Glu Leu Leu Ala Ser Asn Ala Val Ala Val
 290 295 300

Thr Phe Gly Glu Lys Leu Leu Gly Val Met Ala Trp Ile Met Pro Ile
 305 310 315 320

Ser Val Ala Leu Ser Thr Phe Gly Gly Val Asn Gly Ser Leu Phe Thr
 325 330 335

Ser Ser Arg Leu Phe Phe Ala Gly Ala Arg Glu Gly His Leu Pro Ser
 340 345 350

Val Leu Ala Met Ile His Val Lys Arg Cys Thr Pro Ile Pro Ala Leu
 355 360 365

Leu Phe Thr Cys Ile Ser Thr Leu Leu Met Leu Val Thr Ser Asp Met
 370 375 380

Tyr Thr Leu Ile Asn Tyr Val Gly Phe Ile Asn Tyr Leu Phe Tyr Gly
 385 390 395 400

Val Thr Val Ala Gly Gln Ile Val Leu Arg Trp Lys Lys Pro Asp Ile
 405 410 415

Pro Arg Pro Ile Lys Ile Asn Leu Leu Phe Pro Ile Ile Tyr Leu Leu
 420 425 430

Phe Trp Ala Phe Leu Leu Val Phe Ser Leu Trp Ser Glu Pro Val Val
 435 440 445

Cys Gly Ile Gly Leu Ala Ile Met Leu Thr Gly Val Pro Val Tyr Phe
 450 455 460

Leu Gly Val Tyr Trp Gln His Lys Pro Lys Cys Phe Ser Asp Phe Ile
 465 470 475 480

Glu Leu Leu Thr Leu Val Ser Gln Lys Met Cys Val Val Val Tyr Pro
 485 490 495

Glu Val Glu Arg Gly Ser Gly Thr Glu Glu Ala Asn Glu Asp Met Glu
 500 505 510

Glu Gln Gln Gln Pro Met Tyr Gln Pro Thr Pro Thr Lys Asp Lys Asp
 515 520 525

Val Ala Gly Gln Pro Gln Pro
530 535

<210> 112
<211> 466
<212> PRT
<213> Homo sapiens,

<400> 112

Met Thr Leu Lys Ala Ser Glu Gly Glu Ser Gly Gly Ser Met His Thr
1 5 10 15

Ala Leu Ser Asp Leu Tyr Leu Glu His Leu Leu Gln Lys Arg Ser Arg
20 25 30

Pro Glu Ala Val Ser His Pro Leu Asn Thr Val Thr Glu Asp Met Tyr
35 40 45

Thr Asn Gly Ser Pro Ala Pro Gly Ser Pro Ala Gln Val Lys Gly Gln
50 55 60

Glu Val Arg Lys Val Arg Leu Ile Gln Phe Glu Lys Val Thr Glu Glu
65 70 75 80

Pro Met Gly Ile Thr Leu Lys Leu Asn Glu Lys Gln Ser Cys Thr Val
85 90 95

Ala Arg Ile Leu His Gly Gly Met Ile His Arg Gln Gly Ser Leu His
100 105 110

Val Gly Asp Glu Ile Leu Glu Ile Asn Gly Thr Asn Val Thr Asn His
115 120 125

Ser Val Asp Gln Leu Gln Lys Ala Met Lys Glu Thr Lys Gly Met Ile
130 135 140

Ser Leu Lys Val Ile Pro Asn Gln Gln Ser Arg Leu Pro Ala Leu Gln
145 150 155 160

Met Phe Met Arg Ala Gln Phe Asp Tyr Asp Pro Lys Lys Asp Asn Leu
165 170 175

Ile Pro Cys Lys Glu Ala Gly Leu Lys Phe Ala Thr Gly Asp Ile Ile
180 185 190

Gln Ile Ile Asn Lys Asp Asp Ser Asn Trp Trp Gln Gly Arg Val Glu
195 200 205

Gly Ser Ser Lys Glu Ser Ala Gly Leu Ile Pro Ser Pro Glu Leu Gln
 210 215 220

Glu Trp Arg Val Ala Ser Met Ala Gln Ser Ala Pro Ser Glu Ala Pro
 225 230 235 240

Ser Cys Ser Pro Phe Gly Lys Lys Lys Lys Tyr Lys Asp Lys Tyr Leu
 245 250 255

Ala Lys His Ser Ser Ile Phe Asp Gln Leu Asp Val Val Ser Tyr Glu
 260 265 270

Glu Val Val Arg Leu Pro Ala Phe Lys Arg Lys Thr Leu Val Leu Ile
 275 280 285

Gly Ala Ser Gly Val Gly Arg Ser His Ile Lys Asn Ala Leu Leu Ser
 290 295 300

Gln Asn Pro Glu Lys Phe Val Tyr Pro Val Pro Tyr Thr Thr Arg Pro
 305 310 315 320

Pro Arg Lys Ser Glu Glu Asp Gly Lys Glu Tyr His Phe Ile Ser Thr
 325 330 335

Glu Glu Met Thr Arg Asn Ile Ser Ala Asn Glu Phe Leu Glu Phe Gly
 340 345 350

Ser Tyr Gln Gly Asn Met Phe Gly Thr Lys Phe Glu Thr Val His Gln
 355 360 365

Ile His Lys Gln Asn Lys Ile Ala Ile Leu Asp Ile Glu Pro Gln Thr
 370 375 380

Leu Lys Ile Val Arg Thr Ala Glu Leu Ser Pro Phe Ile Val Phe Ile
 385 390 395 400

Ala Pro Thr Asp Gln Gly Thr Gln Thr Glu Ala Leu Gln Gln Leu Gln
 405 410 415

Lys Asp Ser Glu Ala Ile Arg Ser Gln Tyr Ala His Tyr Phe Asp Leu
 420 425 430

Ser Leu Val Asn Asn Gly Val Asp Glu Thr Leu Lys Lys Leu Gln Glu
 435 440 445

Ala Phe Asp Gln Ala Cys Ser Ser Pro Gln Trp Val Pro Val Ser Trp
 450 455 460

Val Tyr
 465

<210> 113
 <211> 393
 <212> PRT
 <213> Homo sapiens

<400> 113

Met Glu Glu Pro Gln Ser Asp Pro Ser Val Glu Pro Pro Leu Ser Gln
 1 5 10 15

Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro Glu Asn Asn Val Leu
 20 25 30

Ser Pro Leu Pro Ser Gln Ala Met Asp Asp Leu Met Leu Ser Pro Asp
 35 40 45

Asp Ile Glu Gln Trp Phe Thr Glu Asp Pro Gly Pro Asp Glu Ala Pro
 50 55 60

Arg Met Pro Glu Ala Ala Pro Pro Val Ala Pro Ala Pro Ala Ala Pro
 65 70 75 80

Thr Pro Ala Ala Pro Ala Pro Ala Pro Ser Trp Pro Leu Ser Ser Ser
 85 90 95

Val Pro Ser Gln Lys Thr Tyr Gln Gly Ser Tyr Gly Phe Arg Leu Gly
 100 105 110

Phe Leu His Ser Gly Thr Ala Lys Ser Val Thr Cys Thr Tyr Ser Pro
 115 120 125

Ala Leu Asn Lys Met Phe Cys Gln Leu Ala Lys Thr Cys Pro Val Gln
 130 135 140

Leu Trp Val Asp Ser Thr Pro Pro Pro Gly Thr Arg Val Arg Ala Met
 145 150 155 160

Ala Ile Tyr Lys Gln Ser Gln His Met Thr Glu Val Val Arg Arg Cys
 165 170 175

Pro His His Glu Arg Cys Ser Asp Ser Asp Gly Leu Ala Pro Pro Gln

180	185	190
His Leu Ile Arg Val Glu Gly Asn Leu Arg Val Glu Tyr Leu Asp Asp		
195	200	205
Arg Asn Thr Phe Arg His Ser Val Val Val Pro Tyr Glu Pro Pro Glu		
210	215	220
Val Gly Ser Asp Cys Thr Thr Ile His Tyr Asn Tyr Met Cys Asn Ser		
225	230	235
Ser Cys Met Gly Gly Met Asn Arg Arg Pro Ile Leu Thr Ile Ile Thr		
	245	250
Leu Glu Asp Ser Ser Gly Asn Leu Leu Gly Arg Asn Ser Phe Glu Val		
	260	265
His Val Cys Ala Cys Pro Gly Arg Asp Arg Arg Thr Glu Glu Glu Asn		
	275	280
Leu Arg Lys Lys Gly Glu Pro His His Glu Leu Pro Pro Gly Ser Thr		
	290	295
Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Ser Pro Gln Pro Lys Lys		
305	310	315
Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu		
	325	330
Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp		
	340	345
Ala Gln Ala Gly Lys Glu Pro Gly Gly Ser Arg Ala His Ser Ser His		
	355	360
Leu Lys Ser Lys Lys Gly Gln Ser Thr Ser Arg His Lys Lys Leu Met		
	370	375
Phe Lys Thr Glu Gly Pro Asp Ser Asp		
385	390	

<210> 114
 <211> 95
 <212> PRT
 <213> Homo sapiens

<400> 114

Met Thr Glu Leu Glu Thr Ala Met Gly Met Ile Ile Asp Val Phe Ser
1 5 10 15

Arg Tyr Ser Gly Ser Glu Gly Ser Thr Gln Thr Leu Thr Lys Gly Glu
20 25 30

Leu Lys Val Leu Met Glu Lys Glu Leu Pro Gly Phe Leu Gln Ser Gly
35 40 45

Lys Asp Lys Asp Ala Val Asp Lys Leu Leu Lys Asp Leu Asp Ala Asn
50 55 60

Gly Asp Ala Gln Val Asp Phe Ser Glu Phe Ile Val Phe Val Ala Ala
65 70 75 80

Ile Thr Ser Ala Cys His Lys Tyr Phe Glu Lys Ala Gly Leu Lys
85 90 95

<210> 115

<211> 120

<212> PRT

<213> Homo sapiens

<400> 115

Met Gly Thr Asn Phe Pro Phe Trp Val Ser Gln Leu Thr Phe Phe Lys
1 5 10 15

Leu Ser Ile Thr Gly Thr Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu
20 25 30

Gly Ile Thr Lys Val Phe Ser Asn Gly Ala Asp Leu Ser Gly Val Thr
35 40 45

Glu Glu Ala Pro Leu Lys Leu Ser Lys Ala Val His Lys Ala Val Leu
50 55 60

Thr Ile Asp Glu Lys Gly Thr Glu Ala Ala Gly Ala Met Phe Leu Glu
65 70 75 80

Ala Ile Pro Met Ser Ile Pro Pro Glu Val Lys Phe Asn Lys Pro Phe
85 90 95

Val Phe Leu Met Ile Glu Gln Asn Thr Lys Ser Pro Leu Phe Met Gly
100 105 110

Lys Val Val Asn Pro Thr Gln Lys
115 120

<210> 116
 <211> 154
 <212> PRT
 <213> Homo sapiens

<400> 116

Met Ala Asp Asp Leu Asp Phe Glu Thr Gly Asp Ala Gly Ala Ser Ala
 1 5 10 15

Thr Phe Pro Met Gln Cys Ser Ala Leu Arg Lys Asn Gly Phe Val Val
 20 25 30

Leu Lys Gly Arg Pro Cys Lys Ile Val Glu Met Ser Thr Ser Lys Thr
 35 40 45

Gly Lys His Gly His Ala Lys Val His Leu Val Gly Ile Asp Ile Phe
 50 55 60

Thr Gly Lys Lys Tyr Glu Asp Ile Cys Pro Ser Thr His Asn Met Asp
 65 70 75 80

Val Pro Asn Ile Lys Arg Asn Asp Phe Gln Leu Ile Gly Ile Gln Asp
 85 90 95

Gly Tyr Leu Ser Leu Leu Gln Asp Ser Gly Glu Val Arg Glu Asp Leu
 100 105 110

Arg Leu Pro Glu Gly Asp Leu Gly Lys Glu Ile Glu Gln Lys Tyr Asp
 115 120 125

Cys Gly Glu Glu Ile Leu Ile Thr Val Leu Ser Ala Met Thr Glu Glu
 130 135 140

Ala Ala Val Ala Ile Lys Ala Met Ala Lys
 145 150

<210> 117
 <211> 519
 <212> PRT
 <213> Homo sapiens

<400> 117

Met Asp Ala Val Leu Glu Pro Phe Pro Ala Asp Arg Leu Phe Pro Gly
 1 5 10 15

Ser Ser Phe Leu Asp Leu Gly Asp Leu Asn Glu Ser Asp Phe Leu Asn

20	25	30
Asn Ala His Phe Pro Glu His Leu Asp His Phe Thr Glu Asn Met Glu		
35	40	45
Asp Phe Ser Asn Asp Leu Phe Ser Ser Phe Phe Asp Asp Pro Val Leu		
50	55	60
Asp Glu Lys Ser Pro Leu Leu Asp Met Glu Leu Asp Ser Pro Thr Pro		
65	70	75
Gly Ile Gln Ala Glu His Ser Tyr Ser Leu Ser Gly Asp Ser Ala Pro		
85	90	95
Gln Ser Pro Leu Val Pro Ile Lys Met Glu Asp Thr Thr Gln Asp Ala		
100	105	110
Glu His Gly Ala Trp Ala Leu Gly His Lys Leu Cys Ser Ile Met Val		
115	120	125
Lys Gln Glu Gln Ser Pro Glu Leu Pro Val Asp Pro Leu Ala Ala Pro		
130	135	140
Ser Ala Met Ala Ala Ala Ala Ala Met Ala Thr Thr Pro Leu Leu Gly		
145	150	155
Leu Ser Pro Leu Ser Arg Leu Pro Ile Pro His Gln Ala Pro Gly Glu		
165	170	175
Met Thr Gln Leu Pro Val Ile Lys Ala Glu Pro Leu Glu Val Asn Gln		
180	185	190
Phe Leu Lys Val Thr Pro Glu Asp Leu Val Gln Met Pro Pro Thr Pro		
195	200	205
Pro Ser Ser His Gly Ser Asp Ser Asp Gly Ser Gln Ser Pro Arg Ser		
210	215	220
Leu Pro Pro Ser Ser Pro Val Arg Pro Met Ala Arg Ser Ser Thr Ala		
225	230	235
Ile Ser Thr Ser Pro Leu Leu Thr Ala Pro His Lys Leu Gln Gly Thr		
245	250	255
Ser Gly Pro Leu Leu Leu Thr Glu Glu Glu Lys Arg Thr Leu Ile Ala		
260	265	270

Glu Gly Tyr Pro Ile Pro Thr Lys Leu Pro Leu Thr Lys Ala Glu Glu
 275 280 285

Lys Ala Leu Lys Arg Val Arg Arg Lys Ile Lys Asn Lys Ile Ser Ala
 290 295 300

Gln Glu Ser Arg Arg Lys Lys Lys Glu Tyr Val Glu Cys Leu Glu Lys
 305 310 315 320

Lys Val Glu Thr Phe Thr Ser Glu Asn Asn Glu Leu Trp Lys Lys Val
 325 330 335

Glu Thr Leu Glu Asn Ala Asn Arg Thr Leu Leu Gln Gln Leu Gln Lys
 340 345 350

Leu Gln Thr Leu Val Thr Asn Lys Ile Ser Arg Pro Tyr Lys Met Ala
 355 360 365

Ala Thr Gln Thr Gly Thr Cys Leu Met Val Ala Ala Leu Cys Phe Val
 370 375 380

Leu Val Leu Gly Ser Leu Val Pro Cys Leu Pro Glu Phe Ser Ser Gly
 385 390 395 400

Ser Gln Thr Val Lys Glu Asp Pro Leu Ala Ala Asp Gly Val Tyr Thr
 405 410 415

Ala Ser Gln Met Pro Ser Arg Ser Leu Leu Phe Tyr Asp Asp Gly Ala
 420 425 430

Gly Leu Trp Glu Asp Gly Arg Ser Thr Leu Leu Pro Met Glu Pro Pro
 435 440 445

Asp Gly Trp Glu Ile Asn Pro Gly Gly Pro Ala Glu Gln Arg Pro Arg
 450 455 460

Asp His Leu Gln His Asp His Leu Asp Ser Thr His Glu Thr Thr Lys
 465 470 475 480

Tyr Leu Ser Glu Ala Trp Pro Lys Asp Gly Gly Asn Gly Thr Ser Pro
 485 490 495

Asp Phe Ser His Ser Lys Glu Trp Phe His Asp Arg Asp Leu Gly Pro
 500 505 510

Asn Thr Thr Ile Lys Leu Ser
515

<210> 118
<211> 534
<212> PRT
<213> Homo sapiens

<400> 118

Met Ala Thr Gly Leu Gln Val Pro Leu Pro Trp Leu Ala Thr Gly Leu
1 5 10 15

Leu Leu Leu Leu Ser Val Gln Pro Trp Ala Glu Ser Gly Lys Val Leu
20 25 30

Val Val Pro Ile Asp Gly Ser His Trp Leu Ser Met Arg Glu Val Leu
35 40 45

Arg Glu Leu His Ala Arg Gly His Gln Ala Val Val Leu Thr Pro Glu
50 55 60

Val Asn Met His Ile Lys Glu Glu Asn Phe Phe Thr Leu Thr Thr Tyr
65 70 75 80

Ala Ile Ser Trp Thr Gln Asp Glu Phe Asp Arg His Val Leu Gly His
85 90 95

Thr Gln Leu Tyr Phe Glu Thr Glu His Phe Leu Lys Lys Phe Phe Arg
100 105 110

Ser Met Ala Met Leu Asn Asn Met Ser Leu Val Tyr His Arg Ser Cys
115 120 125

Val Glu Leu Leu His Asn Glu Ala Leu Ile Arg His Leu Asn Ala Thr
130 135 140

Ser Phe Asp Val Val Leu Thr Asp Pro Val Asn Leu Cys Ala Ala Val
145 150 155 160

Leu Ala Lys Tyr Leu Ser Ile Pro Thr Val Phe Phe Leu Arg Asn Ile
165 170 175

Pro Cys Asp Leu Asp Phe Lys Gly Thr Gln Cys Pro Asn Pro Ser Ser
180 185 190

Tyr Ile Pro Arg Leu Leu Thr Thr Asn Ser Asp His Met Thr Phe Met

195	200	205
Gln Arg Val Lys Asn Met Leu Tyr Pro Leu Ala Leu Ser Tyr Ile Cys 210	215	220
His Ala Phe Ser Ala Pro Tyr Ala Ser Leu Ala Ser Glu Leu Phe Gln 225	230	235 240
Arg Glu Val Ser Val Val Asp Ile Leu Ser His Ala Ser Val Trp Leu 245	250	255
Phe Arg Gly Asp Phe Val Met Asp Tyr Pro Arg Pro Ile Met Pro Asn 260	265	270
Met Val Phe Ile Gly Gly Ile Asn Cys Ala Asn Arg Lys Pro Leu Ser 275	280	285
Gln Glu Phe Glu Ala Tyr Ile Asn Ala Ser Gly Glu His Gly Ile Val 290	295	300
Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu Lys Lys Ala 305	310	315 320
Met Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr Val Leu Trp 325	330	335
Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn Thr Ile Leu 340	345	350
Val Lys Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro Met Thr Arg 355	360	365
Ala Phe Ile Thr His Ala Gly Ser His Gly Val Tyr Glu Ser Ile Cys 370	375	380
Asn Gly Val Pro Met Val Met Met Pro Leu Phe Gly Asp Gln Met Asp 385	390	395 400
Asn Ala Lys Arg Met Glu Thr Lys Gly Ala Gly Val Thr Leu Asn Val 405	410	415
Leu Glu Met Thr Ser Glu Asp Leu Glu Asn Ala Leu Lys Ala Val Ile 420	425	430
Asn Asp Lys Ser Tyr Lys Glu Asn Ile Met Arg Leu Ser Ser Leu His 435	440	445

Lys Asp Arg Pro Val Glu Pro Leu Asp Leu Ala Val Phe Trp Val Glu
 450 455 460

Phe Val Met Arg His Lys Gly Ala Pro His Leu Arg Pro Ala Ala His
 465 470 475 480

Asp Leu Thr Trp Tyr Gln Tyr His Ser Leu Asp Val Ile Gly Phe Leu
 485 490 495

Leu Ala Val Val Leu Thr Val Ala Phe Ile Thr Phe Lys Cys Cys Ala
 500 505 510

Tyr Gly Tyr Arg Lys Cys Leu Gly Lys Lys Gly Arg Val Lys Lys Ala
 515 520 525

His Lys Ser Lys Thr His
 530

<210> 119
 <211> 185
 <212> PRT
 <213> Homo sapiens

<400> 119

Met Ala Met Glu Met Ile Gly Phe Phe Val Arg Leu Ser Ser Ser Leu
 1 5 10 15

Leu Trp Phe Gln Ile Tyr Arg Leu Gly Ala Ala Ile Val Asp Thr Ser
 20 25 30

Leu Pro Arg Glu Thr Asp Ser Asp Leu Arg Asn Ser Phe Leu Asn Pro
 35 40 45

Pro Thr Pro Ala Ile Ala Arg Gln Cys Ser Gly Ala Glu Glu Ile Leu
 50 55 60

Gly Gly Ser Ile Tyr Asp Pro Ala Tyr Tyr Thr Ser Leu Phe Glu Glu
 65 70 75 80

Ser Gln Thr Asn Ile Asn Ser Pro Lys Ala Thr Gln Asp Val His Lys
 85 90 95

Thr Val Arg Ser Asp His Asn Val Val Ile Asn Asp Met Glu Glu Val
 100 105 110

Thr His Pro Met Gln Ile Leu Ser Pro Leu Cys Pro Leu Val Lys Arg

115 120 125
 Ser Gly His Val Thr Lys Trp Asp Cys Ser Asn Thr Val Thr Thr Ser
 130 135 140

 Arg Ala Val His Glu Ile Pro Val Val Glu Phe Ile Arg Asn Phe Asn
 145 150 155 160

 Lys Thr Pro Tyr Ile Leu Asp Asp Leu Glu Arg Ala Pro Leu Trp Thr
 165 170 175

 Met Leu Phe Phe Gly Gly Asn His Lys
 180 185

 <210> 120
 <211> 530
 <212> PRT
 <213> Homo sapiens

 <400> 120

 Met Ala Arg Ala Gly Trp Thr Ser Pro Val Pro Leu Cys Val Cys Leu
 1 5 10 15

 Leu Leu Thr Cys Gly Phe Ala Glu Ala Gly Lys Leu Leu Val Val Pro
 20 25 30

 Met Asp Gly Ser His Trp Phe Thr Met Gln Ser Val Val Glu Lys Leu
 35 40 45

 Ile Leu Arg Gly His Glu Val Val Val Val Met Pro Glu Val Ser Trp
 50 55 60

 Gln Leu Glu Arg Ser Leu Asn Cys Thr Val Lys Thr Tyr Ser Thr Ser
 65 70 75 80

 Tyr Thr Leu Glu Asp Gln Asn Arg Glu Phe Met Val Phe Ala His Ala
 85 90 95

 Gln Trp Lys Ala Gln Ala Gln Ser Ile Phe Ser Leu Leu Met Ser Ser
 100 105 110

 Ser Ser Gly Phe Leu Asp Leu Phe Phe Ser His Cys Arg Ser Leu Phe
 115 120 125

 Asn Asp Arg Lys Leu Val Glu Tyr Leu Lys Glu Ser Ser Phe Asp Ala
 130 135 140

Val Phe Leu Asp Pro Phe Asp Thr Cys Gly Leu Ile Val Ala Lys Tyr
 145 150 155 160

Phe Ser Leu Pro Ser Val Val Phe Thr Arg Gly Ile Phe Cys His His
 165 170 175

Leu Glu Glu Gly Ala Gln Cys Pro Ala Pro Leu Ser Tyr Val Pro Asn
 180 185 190

Asp Leu Leu Gly Phe Ser Asp Ala Met Thr Phe Lys Glu Arg Val Trp
 195 200 205

Asn His Ile Val His Leu Glu Asp His Leu Phe Cys Gln Tyr Leu Phe
 210 215 220

Arg Asn Ala Leu Glu Ile Ala Ser Glu Ile Leu Gln Thr Pro Val Thr
 225 230 235 240

Ala Tyr Asp Leu Tyr Ser His Thr Ser Ile Trp Leu Leu Arg Thr Asp
 245 250 255

Phe Val Leu Asp Tyr Pro Lys Pro Val Met Pro Asn Met Ile Phe Ile
 260 265 270

Gly Gly Ile Asn Cys His Gln Gly Lys Pro Leu Pro Met Glu Phe Glu
 275 280 285

Ala Tyr Ile Asn Ala Ser Gly Glu His Gly Ile Val Val Phe Ser Leu
 290 295 300

Gly Ser Met Val Ser Glu Ile Pro Glu Lys Lys Ala Met Ala Ile Ala
 305 310 315 320

Asp Ala Leu Gly Lys Ile Pro Gln Thr Val Leu Trp Arg Tyr Thr Gly
 325 330 335

Thr Arg Pro Ser Asn Leu Ala Asn Asn Thr Ile Leu Val Lys Trp Leu
 340 345 350

Pro Gln Asn Asp Leu Leu Gly His Pro Met Thr Arg Ala Phe Ile Thr
 355 360 365

His Ala Gly Ser His Gly Val Tyr Glu Ser Ile Cys Asn Gly Val Pro
 370 375 380

Met Val Met Met Pro Leu Phe Gly Asp Gln Met Asp Asn Ala Lys Arg
 385 390 395 400

Met Glu Thr Lys Gly Ala Gly Val Thr Leu Asn Val Leu Glu Met Thr
 405 410 415

Ser Glu Asp Leu Glu Asn Ala Leu Lys Ala Val Ile Asn Asp Lys Ser
 420 425 430

Tyr Lys Glu Asn Ile Met Arg Leu Ser Ser Leu His Lys Asp Arg Pro
 435 440 445

Val Glu Pro Leu Asp Leu Ala Val Phe Trp Val Glu Phe Val Met Arg
 450 455 460

His Lys Gly Ala Pro His Leu Arg Pro Ala Ala His Asp Leu Thr Trp
 465 470 475 480

Tyr Gln Tyr His Ser Leu Asp Val Ile Gly Phe Leu Leu Ala Val Val
 485 490 495

Leu Thr Val Ala Phe Ile Thr Phe Lys Cys Cys Ala Tyr Gly Tyr Arg
 500 505 510

Lys Cys Leu Gly Lys Lys Gly Arg Val Lys Lys Ala His Lys Ser Lys
 515 520 525

Thr His
 530

<210> 121
 <211> 533
 <212> PRT
 <213> Homo sapiens

<400> 121

Met Ala Val Glu Ser Gln Gly Gly Arg Pro Leu Val Leu Gly Leu Leu
 1 5 10 15

Leu Cys Val Leu Gly Pro Val Val Ser His Ala Gly Lys Ile Leu Leu
 20 25 30

Ile Pro Val Asp Gly Ser His Trp Leu Ser Met Leu Gly Ala Ile Gln
 35 40 45

Gln Leu Gln Gln Arg Gly His Glu Ile Val Val Leu Ala Pro Asp Ala
 50 55 60

Ser Leu Tyr Ile Arg Asp Gly Ala Phe Tyr Thr Leu Lys Thr Tyr Pro
65 70 75 80

Val Pro Phe Gln Arg Glu Asp Val Lys Glu Ser Phe Val Ser Leu Gly
85 90 95

His Asn Val Phe Glu Asn Asp Ser Phe Leu Gln Arg Val Ile Lys Thr
100 105 110

Tyr Lys Lys Ile Lys Lys Asp Ser Ala Met Leu Leu Ser Gly Cys Ser
115 120 125

His Leu Leu His Asn Lys Glu Leu Met Ala Ser Leu Ala Glu Ser Ser
130 135 140

Phe Asp Val Met Leu Thr Asp Pro Phe Leu Pro Cys Ser Pro Ile Val
145 150 155 160

Ala Gln Tyr Leu Ser Leu Pro Thr Val Phe Phe Leu His Ala Leu Pro
165 170 175

Cys Ser Leu Glu Phe Glu Ala Thr Gln Cys Pro Asn Pro Phe Ser Tyr
180 185 190

Val Pro Arg Pro Leu Ser Ser His Ser Asp His Met Thr Phe Leu Gln
195 200 205

Arg Val Lys Asn Met Leu Ile Ala Phe Ser Gln Asn Phe Leu Cys Asp
210 215 220

Val Val Tyr Ser Pro Tyr Ala Thr Leu Ala Ser Glu Phe Leu Gln Arg
225 230 235 240

Glu Val Thr Val Gln Asp Leu Leu Ser Ser Ala Ser Val Trp Leu Phe
245 250 255

Arg Ser Asp Phe Val Lys Asp Tyr Pro Arg Pro Ile Met Pro Asn Met
260 265 270

Val Phe Val Gly Gly Ile Asn Cys Leu His Gln Asn Pro Leu Ser Gln
275 280 285

Glu Phe Glu Ala Tyr Ile Asn Ala Ser Gly Glu His Gly Ile Val Val
290 295 300

Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu Lys Lys Ala Met
 305 310 315 320

Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr Val Leu Trp Arg
 325 330 335

Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn Thr Ile Leu Val
 340 345 350

Lys Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro Met Thr Arg Ala
 355 360 365

Phe Ile Thr His Ala Gly Ser His Gly Val Tyr Glu Ser Ile Cys Asn
 370 375 380

Gly Val Pro Met Val Met Met Pro Leu Phe Gly Asp Gln Met Asp Asn
 385 390 395 400

Ala Lys Arg Met Glu Thr Lys Gly Ala Gly Val Thr Leu Asn Val Leu
 405 410 415

Glu Met Thr Ser Glu Asp Leu Glu Asn Ala Leu Lys Ala Val Ile Asn
 420 425 430

Asp Lys Ser Tyr Lys Glu Asn Ile Met Arg Leu Ser Ser Leu His Lys
 435 440 445

Asp Arg Pro Val Glu Pro Leu Asp Leu Ala Val Phe Trp Val Glu Phe
 450 455 460

Val Met Arg His Lys Gly Ala Pro His Leu Arg Pro Ala Ala His Asp
 465 470 475 480

Leu Thr Trp Tyr Gln Tyr His Ser Leu Asp Val Ile Gly Phe Leu Leu
 485 490 495

Ala Val Val Leu Thr Val Ala Phe Ile Thr Phe Lys Cys Cys Ala Tyr
 500 505 510

Gly Tyr Arg Lys Cys Leu Gly Lys Lys Gly Arg Val Lys Lys Ala His
 515 520 525

Lys Ser Lys Thr His
 530

<210> 122
 <211> 318
 <212> PRT
 <213> Homo sapiens

<400> 122

Met Thr Ile Ser Val Glu Lys Pro Ile Phe Glu Glu Glu Val Ser Ala
 1 5 10 15

Phe Glu Lys Ser Gly Asp Asn Ile Gly Glu Leu Lys Leu Asp Gly Gly
 20 25 30

Phe Ser Met Pro Lys Met Asp Thr Asn Asp Asp Glu Ala Phe Leu Ala
 35 40 45

Pro Glu Met Asn Ala Phe Gly Arg Gln Phe Arg Asp Tyr Asp Val Glu
 50 55 60

Ser Glu Arg Gln Lys Gly Val Glu Glu Phe Tyr Arg Leu Gln His Ile
 65 70 75 80

Asn Gln Thr Val Asp Phe Val Lys Lys Met Arg Ala Glu Tyr Gly Lys
 85 90 95

Leu Asp Lys Met Val Met Ser Ile Trp Glu Cys Cys Glu Leu Leu Asn
 100 105 110

Glu Val Val Asp Glu Ser Asp Pro Asp Leu Asp Glu Pro Gln Ile Gln
 115 120 125

His Leu Leu Gln Ser Ala Glu Ala Ile Arg Lys Asp Tyr Pro Asn Glu
 130 135 140

Asp Trp Leu His Leu Thr Ala Leu Ile His Asp Leu Gly Lys Val Ile
 145 150 155 160

Thr Leu Pro Gln Phe Gly Gly Leu Pro Gln Trp Ala Val Val Gly Asp
 165 170 175

Thr Phe Pro Val Gly Cys Ala Phe Asp Glu Ser Asn Val His His Lys
 180 185 190

Tyr Phe Val Glu Asn Pro Asp Phe His Asn Glu Thr Tyr Asn Thr Lys
 195 200 205

Asn Gly Ile Tyr Ser Glu Gly Cys Gly Leu Asn Asn Val Met Met Ser
 210 215 220

Trp Gly His Asp Asp Tyr Met Tyr Leu Val Ala Lys Glu Asn Gly Ser
 225 230 235 240

Thr Leu Pro Ser Ala Gly Gln Phe Ile Ile Arg Tyr His Ser Phe Tyr
 245 250 255

Pro Leu His Thr Ala Gly Glu Tyr Thr His Leu Met Asn Glu Glu Asp
 260 265 270

Lys Glu Asn Leu Lys Trp Leu His Val Phe Asn Lys Tyr Asp Leu Tyr
 275 280 285

Ser Lys Ser Lys Val His Val Asp Val Glu Lys Val Lys Pro Tyr Tyr
 290 295 300

Met Ser Leu Ile Lys Lys Tyr Phe Pro Glu Asn Leu Arg Trp
 305 310 315

<210> 123

<211> 111

<212> PRT

<213> Homo sapiens

<400> 123

Met Ala Asn Ile His Gln Glu Asn Glu Glu Met Glu Gln Pro Met Gln
 1 5 10 15

Asn Gly Glu Glu Asp Arg Pro Leu Gly Gly Gly Glu Gly His Gln Pro
 20 25 30

Ala Gly Asn Arg Arg Gly Gln Ala Arg Arg Leu Ala Pro Asn Phe Arg
 35 40 45

Trp Ala Ile Pro Asn Arg Gln Ile Asn Asp Gly Met Gly Gly Asp Gly
 50 55 60

Asp Asp Met Glu Ile Phe Met Glu Glu Met Arg Glu Ile Arg Arg Lys
 65 70 75 80

Leu Arg Glu Leu Gln Leu Arg Asn Cys Leu Arg Ile Leu Met Gly Glu
 85 90 95

Leu Ser Asn His His Asp His His Asp Glu Phe Cys Leu Met Pro
 100 105 110

<210> 124
 <211> 1516
 <212> PRT
 <213> Homo sapiens

<400> 124

Met Ala Pro Tyr Pro Cys Gly Cys His Ile Leu Leu Leu Leu Phe Cys
 1 5 10 15

Cys Leu Ala Ala Ala Arg Ala Asn Leu Leu Asn Leu Asn Trp Leu Trp
 20 25 30

Phe Asn Asn Glu Asp Thr Ser His Ala Ala Thr Thr Ile Pro Glu Pro
 35 40 45

Gln Gly Pro Leu Pro Val Gln Pro Thr Ala Asp Thr Thr Thr His Val
 50 55 60

Thr Pro Arg Asn Gly Ser Thr Glu Pro Ala Thr Ala Pro Gly Ser Pro
 65 70 75 80

Glu Pro Pro Ser Glu Leu Leu Glu Asp Gly Gln Asp Thr Pro Thr Ser
 85 90 95

Ala Glu Ser Pro Asp Ala Pro Glu Glu Asn Ile Ala Gly Val Gly Ala
 100 105 110

Glu Ile Leu Asn Val Ala Lys Gly Ile Arg Ser Phe Val Gln Leu Trp
 115 120 125

Asn Asp Thr Val Pro Thr Glu Ser Leu Ala Arg Ala Glu Thr Leu Val
 130 135 140

Leu Glu Thr Pro Val Gly Pro Leu Ala Leu Ala Gly Pro Ser Ser Thr
 145 150 155 160

Pro Gln Glu Asn Gly Thr Thr Leu Trp Pro Ser Arg Gly Ile Pro Ser
 165 170 175

Ser Pro Gly Ala His Thr Thr Glu Ala Gly Thr Leu Pro Ala Pro Thr
 180 185 190

Pro Ser Pro Pro Ser Leu Gly Arg Pro Trp Ala Pro Leu Thr Gly Pro
 195 200 205

Ser Val Pro Pro Pro Ser Ser Glu Arg Ile Ser Glu Glu Val Gly Leu
 210 215 220

Leu Gln Leu Leu Gly Asp Pro Pro Pro Gln Gln Val Thr Gln Thr Asp
 225 230 235 240

Asp Pro Asp Val Gly Leu Ala Tyr Val Phe Gly Pro Asp Ala Asn Ser
 245 250 255

Gly Gln Val Ala Arg Tyr His Phe Pro Ser Leu Phe Phe Arg Asp Phe
 260 265 270

Ser Leu Leu Phe His Ile Arg Pro Ala Thr Glu Gly Pro Gly Val Leu
 275 280 285

Phe Ala Ile Thr Asp Ser Ala Gln Ala Met Val Leu Leu Gly Val Lys
 290 295 300

Leu Ser Gly Val Gln Asp Gly His Gln Asp Ile Ser Leu Leu Tyr Thr
 305 310 315 320

Glu Pro Gly Ala Gly Gln Thr His Thr Ala Ala Ser Phe Arg Leu Pro
 325 330 335

Ala Phe Val Gly Gln Trp Thr His Leu Ala Leu Ser Val Ala Gly Gly
 340 345 350

Phe Val Ala Leu Tyr Val Asp Cys Glu Glu Phe Gln Arg Met Pro Leu
 355 360 365

Ala Arg Ser Ser Arg Gly Leu Glu Leu Glu Pro Gly Ala Gly Leu Phe
 370 375 380

Val Ala Gln Ala Gly Gly Ala Asp Pro Asp Lys Phe Gln Gly Val Ile
 385 390 395 400

Ala Glu Leu Lys Val Arg Arg Asp Pro Gln Val Ser Pro Met His Cys
 405 410 415

Leu Asp Glu Glu Gly Asp Asp Ser Asp Gly Ala Phe Gly Asp Ser Gly
 420 425 430

Ser Gly Leu Gly Asp Ala Arg Glu Leu Leu Arg Glu Glu Thr Gly Ala
 435 440 445

Ala Leu Lys Pro Arg Leu Pro Ala Pro Pro Pro Val Thr Thr Pro Pro
 450 455 460

Leu Ala Gly Gly Ser Ser Thr Glu Asp Ser Arg Ser Glu Glu Val Glu
 465 470 475 480

Glu Gln Thr Thr Val Ala Ser Leu Gly Ala Gln Thr Leu Pro Gly Ser
 485 490 495

Asp Ser Val Ser Thr Trp Asp Gly Ser Val Arg Thr Pro Gly Gly Arg
 500 505 510

Val Lys Glu Gly Gly Leu Lys Gly Gln Lys Gly Glu Pro Gly Val Pro
 515 520 525

Gly Pro Pro Gly Arg Ala Gly Pro Pro Gly Ser Pro Cys Leu Pro Gly
 530 535 540

Pro Pro Gly Leu Pro Cys Pro Val Ser Pro Leu Gly Pro Ala Gly Pro
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Ala Leu Gln Thr Val Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly
 565 570 575

Arg Asp Gly Thr Pro Gly Arg Asp Gly Glu Pro Gly Asp Pro Gly Glu
 580 585 590

Asp Gly Lys Pro Gly Asp Thr Gly Pro Gln Gly Phe Pro Gly Thr Pro
 595 600 605

Gly Asp Val Gly Pro Lys Gly Asp Lys Gly Asp Pro Gly Val Gly Glu
 610 615 620

Arg Gly Pro Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly Pro Ser
 625 630 635 640

Phe Arg His Asp Lys Leu Thr Phe Ile Asp Met Glu Gly Ser Gly Phe
 645 650 655

Gly Gly Asp Leu Glu Ala Leu Arg Gly Pro Arg Gly Phe Pro Gly Pro
 660 665 670

Pro Gly Pro Pro Gly Val Pro Gly Leu Pro Gly Glu Pro Gly Arg Phe
 675 680 685

Gly Val Asn Ser Ser Asp Val Pro Gly Pro Ala Gly Leu Pro Gly Val
 690 695 700

Pro Gly Arg Glu Gly Pro Pro Gly Phe Pro Gly Leu Pro Gly Pro Pro
 705 710 715 720

Gly Pro Pro Gly Arg Glu Gly Pro Pro Gly Arg Thr Gly Gln Lys Gly
 725 730 735

Ser Leu Gly Glu Ala Gly Ala Pro Gly His Lys Gly Ser Lys Gly Ala
 740 745 750

Pro Gly Pro Ala Gly Ala Arg Gly Glu Ser Gly Leu Ala Gly Ala Pro
 755 760 765

Gly Pro Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly
 770 775 780

Pro Gly Leu Pro Ala Gly Phe Asp Asp Met Glu Gly Ser Gly Gly Pro
 785 790 795 800

Phe Trp Ser Thr Ala Arg Ser Ala Asp Gly Pro Gln Gly Pro Pro Gly
 805 810 815

Leu Pro Gly Leu Lys Gly Asp Pro Gly Val Pro Gly Leu Pro Gly Ala
 820 825 830

Lys Gly Glu Val Gly Ala Asp Gly Ile Pro Gly Phe Pro Gly Leu Pro
 835 840 845

Gly Arg Glu Gly Ile Ala Gly Pro Gln Gly Pro Lys Gly Asp Arg Gly
 850 855 860

Ser Arg Gly Glu Lys Gly Asp Pro Gly Lys Asp Gly Val Gly Gln Pro
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Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Val Val Tyr Val Ser
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Glu Gln Asp Gly Ser Val Leu Ser Val Pro Gly Pro Glu Gly Arg Pro
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Gly Phe Ala Gly Phe Pro Gly Pro Ala Gly Pro Lys Gly Asn Leu Gly
 915 920 925

Ser Lys Gly Glu Arg Gly Ser Pro Gly Pro Lys Gly Glu Lys Gly Glu
 930 935 940

Pro Gly Ser Ile Phe Ser Pro Asp Gly Gly Ala Leu Gly Pro Ala Gln

945

950

955

960

Lys Gly Ala Lys Gly Glu Pro Gly Phe Arg Gly Pro Pro Gly Pro Tyr
965 970 975

Gly Arg Pro Gly Tyr Lys Gly Glu Ile Gly Phe Pro Gly Arg Pro Gly
980 985 990

Arg Pro Gly Met Asn Gly Leu Lys Gly Glu Lys Gly Glu Pro Gly Asp
995 1000 1005

Ala Ser Leu Gly Phe Gly Met Arg Gly Met Pro Gly Pro Pro Gly
1010 1015 1020

Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Thr	Pro	Val	Tyr	Asp	Ser
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Asn Val  Phe Ala Glu Ser Ser  Arg Pro Gly Pro Pro  Gly Leu Pro
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Gly Asn Gln Gly Pro Pro Gly Pro Lys Gly Ala Lys Gly Glu Val
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Gly Pro Pro Gly Pro Pro Gly Gln Phe Pro Phe Asp Phe Leu Gln
1070 1075 1080

Leu Glu Ala Glu Met Lys Gly Glu Lys Gly Asp Arg Gly Asp Ala
1085 1090 1095

Gly Gln Lys Gly Glu Arg Gly Glu Pro Gly Gly Gly Gly Phe Phe
1100 1105 1110

Gly Ser Ser Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Arg Gly
1115 1120 1125

Tyr Pro Gly Ile Pro Gly Pro Lys Gly Glu Ser Ile Arg Gly Gln
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Pro Gly Pro Pro Gly Pro Gln Gly Pro Pro Gly Ile Gly Tyr Glu
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Gly Arg Gln Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro
1160 1165 1170

Ser Phe Pro Gly Pro His Arg Gln Thr Ile Ser Val Pro Gly Pro
1175 1180 1185

Pro Gly 1190	Pro Pro Gly Pro Pro Gly Thr 1195	Met Gly Ala 1200
Ser Ser 1205	Gly Val Arg Leu Trp 1210	Ala Thr Arg Gln Ala Met Leu Gly 1215
Gln Val 1220	His Glu Val Pro Glu 1225	Gly Trp Leu Ile Phe Val Ala Glu 1230
Gln Glu 1235	Glu Leu Tyr Val Arg 1240	Val Gln Asn Gly Phe Arg Lys Val 1245
Gln Leu 1250	Glu Ala Arg Thr Pro 1255	Leu Pro Arg Gly Thr Asp Asn Glu 1260
Val Ala 1265	Ala Leu Gln Pro Pro 1270	Val Val Gln Leu His Asp Ser Asn 1275
Pro Tyr 1280	Pro Arg Arg Glu His 1285	Pro His Pro Thr Ala Arg Pro Trp 1290
Arg Ala 1295	Asp Asp Ile Leu Ala 1300	Ser Pro Pro Arg Leu Pro Glu Pro 1305
Gln Pro 1310	Tyr Pro Gly Ala Pro 1315	His His Ser Ser Tyr Val His Leu 1320
Arg Pro 1325	Ala Arg Pro Thr Ser 1330	Pro Pro Ala His Ser His Arg Asp 1335
Phe Gln 1340	Pro Val Leu His Leu 1345	Val Ala Leu Asn Ser Pro Leu Ser 1350
Gly Gly 1355	Met Arg Gly Ile Arg 1360	Gly Ala Asp Phe Gln Cys Phe Gln 1365
Gln Ala 1370	Arg Ala Val Gly Leu 1375	Ala Gly Thr Phe Arg Ala Phe Leu 1380
Ser Ser 1385	Arg Leu Gln Asp Leu 1390	Tyr Ser Ile Val Arg Arg Ala Asp 1395
Arg Ala 1400	Ala Val Pro Ile Val 1405	Asn Leu Lys Asp Glu Leu Leu Phe 1410

Pro Ser Trp Glu Ala Leu Phe Ser Gly Ser Glu Gly Pro Leu Lys
 1415 1420 1425

Pro Gly Ala Arg Ile Phe Ser Phe Asp Gly Lys Asp Val Leu Arg
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His Pro Thr Trp Pro Gln Lys Ser Val Trp His Gly Ser Asp Pro
 1445 1450 1455

Asn Gly Arg Arg Leu Thr Glu Ser Tyr Cys Glu Thr Trp Arg Thr
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Glu Ala Pro Ser Ala Thr Gly Gln Ala Ser Ser Leu Leu Gly Gly
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Arg Leu Leu Gly Gln Ser Ala Ala Ser Cys His His Ala Tyr Ile
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Val Leu Cys Ile Glu Asn Ser Phe Met Thr Ala Ser Lys
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 <211> 684
 <212> PRT
 <213> Homo sapiens

<400> 125

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Gly Gln Leu Leu Ala Ala Ala Gly Ala Gln Arg Val Gly Leu Pro Gly
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Pro Pro Gly Pro Pro Gly Arg Pro Gly Lys Pro Gly Gln Asp Gly Ile
 35 40 45

Asp Gly Glu Ala Gly Pro Pro Gly Leu Pro Gly Pro Pro Gly Pro Lys
 50 55 60

Gly Ala Pro Gly Lys Pro Gly Lys Pro Gly Glu Ala Gly Leu Pro Gly
 65 70 75 80

Leu Pro Gly Val Asp Gly Leu Thr Gly Arg Asp Gly Pro Pro Gly Pro
 85 90 95

Lys Gly Ala Pro Gly Glu Arg Gly Ser Leu Gly Pro Pro Gly Pro Pro

100					105					110									
Gly	Leu	Gly	Gly	Lys	Gly	Leu	Pro	Gly	Pro	Pro	Gly	Glu	Ala	Gly	Val				
115					120					125									
Ser	Gly	Pro	Pro	Gly	Gly	Ile	Gly	Leu	Arg	Gly	Pro	Pro	Gly	Pro	Pro				
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Gly	Leu	Pro	Gly	Leu	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly				
145					150					155					160				
His	Pro	Gly	Val	Leu	Pro	Glu	Gly	Ala	Thr	Asp	Leu	Gln	Cys	Pro	Ser				
165					170					175									
Ile	Cys	Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Met	Pro	Gly	Phe	Lys				
180					185					190									
Gly	Pro	Thr	Gly	Tyr	Lys	Gly	Glu	Gln	Gly	Glu	Val	Gly	Lys	Asp	Gly				
195					200					205									
Glu	Lys	Gly	Asp	Pro	Gly	Pro	Pro	Gly	Pro	Ala	Gly	Leu	Pro	Gly	Ser				
210					215					220									
Val	Gly	Leu	Gln	Gly	Pro	Arg	Gly	Leu	Arg	Gly	Leu	Pro	Gly	Pro	Leu				
225					230					235					240				
Gly	Pro	Pro	Gly	Asp	Arg	Gly	Pro	Ile	Gly	Phe	Arg	Gly	Pro	Pro	Gly				
245					250					255									
Ile	Pro	Gly	Ala	Pro	Gly	Lys	Ala	Gly	Asp	Arg	Gly	Glu	Arg	Gly	Pro				
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Glu	Gly	Phe	Arg	Gly	Pro	Lys	Gly	Asp	Leu	Gly	Arg	Pro	Gly	Pro	Lys				
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Gly	Thr	Pro	Gly	Val	Ala	Gly	Pro	Ser	Gly	Glu	Pro	Gly	Met	Pro	Gly				
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Lys	Asp	Gly	Gln	Asn	Gly	Val	Pro	Gly	Leu	Asp	Gly	Gln	Lys	Gly	Glu				
305					310					315					320				
Ala	Gly	Arg	Asn	Gly	Ala	Pro	Gly	Glu	Lys	Gly	Pro	Asn	Gly	Leu	Pro				
325					330					335									
Gly	Leu	Pro	Gly	Arg	Ala	Gly	Ser	Lys	Gly	Glu	Lys	Gly	Glu	Arg	Gly				
340					345					350									

Arg Ala Gly Glu Leu Gly Glu Ala Gly Pro Ser Gly Glu Pro Gly Val
 355 360 365

Pro Gly Asp Ala Gly Met Pro Gly Glu Arg Gly Glu Ala Gly His Arg
 370 375 380

Gly Ser Ala Gly Ala Leu Gly Pro Gln Gly Pro Pro Gly Ala Pro Gly
 385 390 395 400

Val Arg Gly Phe Gln Gly Gln Lys Gly Ser Met Gly Asp Pro Gly Leu
 405 410 415

Pro Gly Pro Gln Gly Leu Arg Gly Asp Val Gly Asp Arg Gly Pro Gly
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Gly Ala Glu Gly Pro Lys Gly Asp Gln Gly Ile Ala Gly Ser Asp Gly
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Leu Pro Gly Asp Lys Gly Glu Leu Gly Pro Ser Gly Leu Val Gly Pro
 450 455 460

Lys Gly Glu Ser Gly Ser Arg Gly Glu Leu Gly Pro Lys Gly Thr Gln
 465 470 475 480

Gly Pro Asn Gly Thr Ser Gly Val Gln Gly Val Pro Gly Pro Pro Gly
 485 490 495

Pro Leu Gly Leu Gln Gly Val Pro Gly Val Pro Gly Ile Thr Gly Lys
 500 505 510

Pro Gly Val Pro Gly Lys Glu Ala Ser Glu Gln Arg Ile Arg Glu Leu
 515 520 525

Cys Gly Gly Met Ile Ser Glu Gln Ile Ala Gln Leu Ala Ala His Leu
 530 535 540

Arg Lys Pro Leu Ala Pro Gly Ser Ile Gly Arg Pro Gly Pro Ala Gly
 545 550 555 560

Pro Pro Gly Pro Pro Gly Pro Pro Gly Ser Ile Gly His Pro Gly Ala
 565 570 575

Arg Gly Pro Pro Gly Tyr Arg Gly Pro Thr Gly Glu Leu Gly Asp Pro
 580 585 590

Gly Pro Arg Gly Asn Gln Gly Asp Arg Gly Asp Lys Gly Ala Ala Gly
595 600 605

Ala Gly Leu Asp Gly Pro Glu Gly Asp Gln Gly Pro Gln Gly Pro Gln
610 615 620

Gly Val Pro Gly Thr Ser Lys Asp Gly Gln Asp Gly Ala Pro Gly Glu
625 630 635 640

Pro Gly Pro Pro Gly Asp Pro Gly Leu Pro Gly Ala Ile Gly Ala Gln
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Gly Thr Pro Gly Ile Cys Asp Thr Ser Ala Cys Gln Gly Ala Val Leu
660 665 670

Gly Gly Val Gly Glu Lys Ser Gly Ser Arg Ser Ser
675 680